STAndardised DIagnostic Assessment for children and adolescents with emotional difficulties (STADIA): a multi-centre randomised controlled trial

Health Economic Analysis Plan (HEAP)

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Contents

1. Trial summary

Title	STAndardised DIagnostic Assessment for children and adolescents with emotional difficulties (STADIA)
Trial Design	Multi-centre, two-arm, parallel group, randomised controlled trial (RCT).
Objectives	The aim of the study is to evaluate the clinical and cost effectiveness of a standardised diagnostic assessment (SDA) tool as an adjunct to usual clinical care in children and adolescents presenting with emotional difficulties referred to Child and Adolescent Mental Health Services (CAMHS). Additionally, the study will: Include a detailed qualitative component to address: a) the feasibility of recruitment; b) the acceptability and usability of the interventions and procedure; c) how the intervention is used and how this deployment could be refined. Seek to optimise the design and delivery of the SDA tool in partnership with young people, parents and CAMHS professionals to enhance acceptability, effectiveness and long-term uptake. Identify the barriers and facilitators to implementation from the perspective of patients, parents, and CAMHS practitioners, managers and commissioners. Use the knowledge gained to make evidence-based recommendations for assessment procedures within CAMHS and produce practice guidelines for clinical decision-making around the referral acceptance and assessment processes.
Participant Population and Key Eligibility Criteria	*Population*: Children and young people (age 5-17 years) presenting with emotional difficulties referred to Child and Adolescent Mental Health Services (CAMHS) *Inclusion criteria for the child/young person* Aged 5 to 17 years. Referred to outpatient multidisciplinary specialist CAMHS. Presenting with emotional difficulties. If aged <16, has an eligible individual with parental responsibility (the parent/carer – see eligibility criteria below) willing and able to participate in the trial. If aged 16-17, has capacity to provide valid written informed consent. If aged 16-17 and participating without a parent/carer, able to complete the assessment tool in English. If aged 16-17 and participating without a parent/carer, access to internet and email or telephone. *Exclusion criteria for the child/young person* Emergency or urgent referral to outpatient multidisciplinary specialist CAMHS (i.e. requires an expedited assessment) according to local risk assessment procedures. Child has severe learning disability. Previously randomised in the STADIA trial. *Inclusion criteria for the parent/carer* Individual with parental responsibility for the child/young person referred to CAMHS. Adequate knowledge of the child/young person to be able to complete the assessment tool (i.e., known for at least 6 months). Has capacity to provide valid written informed consent. Access to internet and email or telephone. Able to complete the assessment tool in English. *Exclusion criteria for the parent/carer* Local authority representatives designated to care for the child/young person.
Intervention and control	*Intervention*: The intervention is a standardised diagnostic assessment (SDA) tool as an adjunct to usual clinical care. The SDA tool will be the Development and Well-Being Assessment (DAWBA). The DAWBA will be completed by the parent (and child, if aged 11+) before the referral has been accepted and a summary report will be provided to participants and clinical staff, as an adjunct to usual clinical practice. *Control*: Children and young people randomised to the comparator arm will receive usual care (i.e., referral review as usual). Based on standard information provided with

	the referral a clinical decision is made about whether the referral is accepted and, if so, a clinician conducts the initial CAMHS assessment as per usual practice in the service.

2. Purpose of HEAP

Confirmation about the presence (a clinical diagnosis) or absence of an emotional disorder could have a major impact on the lives of the young person and their parent/carer, whereby confirmation of a diagnosis could enable the start of an appropriate evidence-based intervention regime and additionally give participants some level of understanding about their difficulties and what they might be facing. Equally, ruling out a diagnosis could provide reassurance and enable signposting to alternative support so that they move forward. Both outcomes potentially have large implications for patient health related quality of life (HRQoL) and their health care resource use across the trial period in addition to across the lifecourse. The aim of this HEAP is to lay out the design and analytical methods which will be used to quantify these implications, and so evaluate the cost effectiveness of the STADIA trial intervention compared to usual care at twelve months post-randomisation. The methods specified in this document are prospective and are subject to change in line with the recommendations of official bodies and/or guidelines of best practice. Completion rates of health economic measures may require further assumptions or analyses.

NB Health Economic HEAPs are fluid documents and whilst a potential structure for analysis, are subject to change. Some elements of the HEAP are aspirational rather than NIHR requirements.

3. Economic perspective

In accordance with NICE guidance, the primary analysis will take an NHS and personal social services perspective (National Institute for Health and Care Excellence, 2013). Parallel analysis will take a broader approach using a societal perspective.

4. Economic Data and Management

4.1 Software

All data will be imported from Microsoft Excel and analysed in StataSE (Release 16; StataCorp, USA).

4.2 Data cleaning

Plausibility checks will be performed on data fields relevant to the economic evaluation of the trial. For example, a participant reporting >30 inpatient hospital admissions within a three-month period may be considered implausible. More extreme examples, such as triple digit service use, are likely impossible and may be a result of transcription error or participant confusion. Where problems are identified, the health economic analyst will contact the data manager and/or other relevant members of staff for clarification and/or further investigation.

4.3 Outcomes

Primary outcomes	Measurement	Technical notes
Health related quality of life for parent/carer	EuroQoL-5D five level (5L) version. (Herdmand et al., 2011). Completed by the parent/carer at baseline, six months, and twelve months.	A multi attribute utility instrument, recommended by the National Institute for Health and Care Excellence (NICE), for estimating health related quality of life. In addition to a descriptive profile, the EQ-5D may produce a single index value for health status. The EQ-5D health state utility score is derived from five individual items (domains) with five response levels, which when combined with a suitable valuation set (representing societal preferences), produces a cardinal index value ranging from -0.59 to 1, with 0 representing death, 1 of-perfect health, and <0 of health states worse than death. The EQ-5D instrument includes the EuroQol Visual Analogue Scale (EQ-VAS), where recipients self-assess their health state 'today' and is rated on a scale from 0 (worst imaginable health) to 100 (best imaginable health). Following an official statement of position there is no recommended population tariff available for the EQ-5D (National Institute for Health and Care Excellence, 2019). The EQ-5D-L may be mapped to the EQ-5D-3L while a new tariff is under development. If missingness can be predicted through observed data, such as demographics or clinical measurements, then methods of multiple imputation will be applied using available case data. See ***5. Procedures for missing data*** for more information.
Health related quality of life for the child/young person	EQ-5D-Y (Youth). (Wille et al., 2010). Completed by young people aged 11 and over. Proxy versions will also be completed by the parent/carer at baseline, six months, and twelve months.	A child-friendly version of the EQ-5D, where the wording of the questionnaire was adapted so that the EQ-5D dimensions were appropriate for the measurement of health related quality of life in young people. The EQ-5D-Y provides a descriptive profile. While validated in young people (Ravens et al., 2010), further testing is recommended since no valuation set is currently available from a young person perspective. Some studies have utilised the tariff of the adult version of the EQ-5D to derive index values. A proxy report will be used for participants aged between 5-15, while for participants aged 16-17 the results from the young adults EQ-5D-Y will be used. Further analysis could be carried out comparing the proxy report of the 5-15 year olds to the 16-17 age group

Health related quality of life for the child/young person	Child Health Utility 9 Dimensions (CHU9D). (Stevens, 2009). Completed by young people aged 11 and over at baseline, six months, and twelve months. Proxy versions will also be completed by the parent/carer.	A paediatric generic preference-based measure of health related quality of life. The CHU9D questionnaire consists of nine individual items with five levels of response per question. The CHU9D provides a descriptive profile and offers a specific adult-elicited valuation set for the derivation of the index (Stevens, 2012).

Secondary outcomes	**Measurement**	**Technical notes**
Confirmed diagnosis decision	Extracted from CAMHS administrative records.	Diagnosis of an emotional disorder will be coded as 'yes'; absence or uncertainty (for example, reflecting ongoing assessment or investigation) about the presence of an emotional disorder will be coded as 'no'. Eligible diagnoses are those that reflect 'emotional' or 'internalizing' disorders in ICD/DSM.
Acceptance of any Referral within 12 months	Extracted from CAMHS administrative records.	Whether the index referral or any subsequent referral to CAMHS (if made) was accepted or not. Acceptance is defined as being offered an appointment within CAMHS, whether or not the initial appointment was attended or subsequent appointments were offered/attended.
Potential additional analysis may occur at the 18 month time point regarding confirmed diagnosis and acceptance of referral and changes from the 12 month time point	Extracted from CAMHS administrative records. Extracted from CAMHS administrative records.	Please note this suggested analysis is not funded within the health economics study and will only occur if additional time/funding can be found to facilitate this.

4.4 Derivation of indices of HRQoL and quality adjusted life years

Indices of HRQoL for the EQ-5D, EQ-5D-Y, and CHU9D will be derived using relevant population tariffs. If a suitable tariff is not available for the EQ-5D five level (5L) version by trial data-lock then the 5L responses will be mapped to the 3L variant so that an established UK valuation set may be used.

We note that adult tariffs may differ to young people in their attribution of different weights to profile states of HRQoL and additionally that the use of child and adult-proxy measures may produce multimodal distributions of health state utilities. For further discussion Donna et al. (2020) provides a good review of the matter alongside confirmatory analysis of the psychometric properties, validity, and suitability of our applied instruments.

EQ-VAS scores represent individual rather than societal preferences, and as such do not require a valuation set. These scores will be divided by 100 before QALY construction to ease comparison with other administered HRQoL instruments.

Area under the curve (AUC) will be used to adjust participant HRQoL for the time spent in their respective health states, constructing quality adjusted life-years (QALYs).

4.5 Health care and other resource use

Data will be collected on health care, education, and social care resource use using a purposely designed resource use collection tool at six and twelve months. The questionnaire, developed by health economists and the wider study team with feedback from patient and public involvement groups, addresses primary, secondary, and social care costs, alongside broader patient-borne costs. These data will be attributable to the emotional difficulties of the young person and be self-reported by the parent/carer with further information obtained from young people aged 16 and 17. In the pre 16 / 17 old group, resource use data is only collected from the parents / carers. Administrative records of treatments/interventions offered by CAMHS during the trial period may be considered as a supplementary source of data.

4.6 Costing of resource use

All costs will be brought to the current values, as of date of trial data lock, through inflationary rates drawn from the consumer inflation series [Office for National Statistics, 2020] where necessitated; direct-to-NHS costs utilising those for Medical Services and Paramedical Services, and societal costs the average consumer tariff.

Resource use	**Costing sources and technical notes**
	Direct intervention costs
The DAWBA questionnaire and administration	The costs associated with the DAWBA and its administration are difficult to measure with precision but are expected to be small, where: RA time – this would be an NHS Administrator (and their time) if done in a real-world clinical setting The time for clinician inspection of the DAWBA is subsumed by the regular appointment session of the young person and so captured within the costs of CAMHS visits. Furthermore, since the trial is an examination of not only the diagnostic value of the DAWBA, but also of clinician behaviours themselves, we cannot directly ensure that the clinicians read the results that are made available to them, nor can we observe this data without introducing bias and interacting with each individual clinician. Therefore, the applicable costs to the NHS are those directly for the DAWBA package. The current charge for an online DAWBA assessment is £10 per individual, which will be added as a fixed cost per each young person in the trial. https://www.dawba.info/f0.html (Youthinmind, 2016). On the participant side, there likely exists a significant patient/carer burden of the time taken to complete the DAWBA measures by the young person and parent/carer. However, the online assessment, as informed by feedback from PPI groups and their working constraints, falls outside of working hours and as such represent no productivity losses. The qualitative research revealed that forms are filled in during participants leisure time and as such a value of 25% average wage rate could be used.
	NHS costs
NHS inpatient admissions	The National Cost Collection (NHS Improvement, 2020)
NHS outpatient visits and primary/community services	Unit Costs of Health and Social Care (Curtis & Burns, 2019)

Societal costs	
Productivity losses	The costs of absenteeism will be estimated through the lost wages approach including a suitable team multiplier (Mattke et al., 2007; Nicholson et al., 2003); where reports of health-related time taken off work will be combined with population-level gross weekly salaries from the Annual Survey of Hours and Earnings (Office for National Statistics, 2019), stratified by full/part-time employment status, age, and gender.
Out-of-pocket expenses	Participant self-reports of costs will be used for travel, parking, private healthcare visits, private prescriptions. Receipt of NHS prescriptions will utilise costs drawn from The British National Formulary (Joint Formulary Committee 2020)
Educational resources	In addition to time off education, the proforma collects further data such as a young person's use of an after-school club or teaching assistant, and meetings with SENDCO (Special Education Needs & Disabilities Co-ordinator), head of year, or school counsellor. Other use is also requested as an open-ended question. These resources, while not traditionally considered within CEA, will be costed using staffing bands and assumptions of duration of contact, or other appropriate unit costs where available.

5. Procedures for Missing Data

Handling of missing data will follow guidelines for intention to treat analysis with incomplete observations (White et al., 2011a). Tests of missingness mechanisms will be conducted to determine the feasibility of the missing at random (MAR) assumption. If missingness can be predicted through observed data, such as demographics or clinical measurements, then methods of multiple imputation will be applied using available case data, such as Multiple Imputation of Chained Equations (MICE), which build into their models the inherent uncertainty associated with the missing data; specifying a separate conditional distribution for each imputed variable (Royston & White, 2011; White et al., 2011b). Otherwise, methodologies which do not presume MAR will be employed. The number of multiply imputed sets generated will equal the % of non-complete cases/total sample size (Graham et al., 2007). MICE will be run multiple times and multiply imputed distributions visually inspected to confirm the robustness of parameter estimates.

Importantly, a confirmed CAMHs diagnosis decision cannot exist outside of the care setting and observation (unlike patient HRQoL which may have held constant, worsened, or improved).

6. Within-trial Analysis

6.1 Population and time horizon

The economic evaluation will take an incremental approach between the two groups using an intention-to-treat (ITT) population (irrespective of treatment received) and a 12-month time horizon.

6.2 Discount rates
No discounting will be applied to derived QALYs or costs due to their being incurred within a twelve-month period.

6.3 Analysis of outcomes and resource use
HRQoL outcomes and QALYs, alongside healthcare service use and derived costs, will be summarily presented for each arm of the trial. 95% confidence intervals will be estimated through the non-parametric method of bootstrapping in lieu of standard deviations due to the heavy-tailed distributions of count data, and the frequent multi-modal distributions (in addition to ceiling and floor effects) of HRQoL indices and their subsequently derived QALYs.

The outcome for the primary cost utility analysis will be the joint QALYs of the young person and parent/carer using the EQ-5D, EQ-5D-Y, and CHU9D. The outcome for the secondary cost effectiveness analysis will utilise the primary outcome of the STADIA trial of a confirmed diagnosis decision. Outcomes will then be jointly analysed as paired units with their direct-to-NHS costs, and more broadly societal costs.

Between-arm differences will be estimated through methods such as seemingly unrelated regressions (SUR), which is a simultaneous method permitting baseline and covariate adjustment such as multicentre effects, while capturing the multivariate distributions of outcomes through allowing correlation between the error terms of regressions (Davidson et al., 1993). QALY regressions will include a continuous variable for HRQoL at baseline, since imbalances have been shown to confound estimates of incremental QALYs, regardless of statistical significance (Manca et al., 2005).

6.4 Sampling uncertainty
The regression-based estimates of mean differences will be bootstrapped to derive 95% confidence intervals, and resultant point estimates used to construct incremental cost effectiveness ratios (ICERS), where:

$$ICER = \frac{\Delta Cost}{\Delta QALY} = \frac{Cost_{Intervention} - Cost_{TAU}}{QALY_{Intervention} - QALY_{TAU}}$$

These will be scattered on the cost effectiveness plane to visually represent sampling uncertainty.

Cost Effectiveness Acceptability Curves (CEACs) will then be constructed using the net monetary benefit framework, which represents the monetary value to the NHS when the willingness-to-pay threshold (λ) for a specified outcome is known (Hoch et al., 2002), where:

$$INMB = (\lambda * \Delta Outcome) - (Cost_{Intervention} - Cost_{TAU})$$

By rearranging the decision rule, where a treatment is cost effective if the incremental cost effectiveness ratio (ICER) is less than the threshold, a therapy should be adopted if the incremental net monetary benefit>0. Accordingly, we will derive an INMB across a range of thresholds for each bootstrapped iteration of the multivariate distributions of incremental outcome and costs. The resulting plot will present the non-parametric proportion (probability) cost effective (0-100%) of the DAWBA intervention by willingness-to-pay thresholds for one QALY (primary CUA) or confirmed diagnosis decision (secondary CEA).

6.5 Subgroup analyses
Owing to no explicit design for inference in economic outcomes, we will not be conducting subgroup CUA or CEA which would present additional sample size concerns.

6.6 Sensitivity analyses

- Analysis applied to complete case data, alongside their multiply imputed counterparts, if more than 10% of data is missing. Other strategies may involve worst/best case assumptions for HRQoL.

- While the CUA will adjust for baseline HRQoL, unadjusted estimates and further multivariate adjustments (such as multicentre effects in the case of costs) may be reported if such effects are observed.

- As a diagnostic intervention the analysis of costs are affected by numerous assumptions depending on the perspective a decision maker may wish to take given the 12-month trial period. The time horizon was designed for inference of confirmed diagnosis decisions by end of trial. Importantly, an economic evaluation measuring resource use will inherently measure the costs associated with the intervention and not the incremental cost to achieve a confirmed diagnosis decision. In example, we would capture the costs of a participant's treatments following a confirmed diagnosis or the reduced burden on other parts of the system through possible reduced acute events. Arguably the CUA measuring HRQoL would capture any early benefits of treatment and therefore should include the costs of all resource use, however it presents issues for the secondary CEA using the outcome of confirmed diagnosis decision. Therefore, we may conduct further costing scenarios using only the resource use of the DAWBA, the DAWBA + CAHMS appointments, or the DAWBA + CAMHS appointments up to the point of a confirmed diagnosis decision or the end of trial period if no decision is recorded.
- The trial has gained an extension to complete diagnosis outcome at 12 and 18 months as such the health economic analysis will now use both end points. Primary analysis will be per protocol at 12 months. Secondary analysis will be conducted at 18 months using the study extension where funding and time allows as the 18month period does not fund continuation of health economics elements.
- The conditions across the country resulting from the COVID-19 pandemic presents issues for the true measurement of health care resource use and their derived costs. While most other measures (such as clinical outcomes) within an RCT could assume that effects would be balanced between trial arms and so cancel out, this assumption cannot be upheld for resource use. From quarantine orders and the repurposing of health care staff, to the more intrinsic effects on human behaviour, the crisis has greatly reduced access to and receipt of health care services. Given there is a hard floor effect of zero item-level health care service use, even if the intervention were to reduce the resource use of participants (or vice versa), the control arm may already be using so few resources that we may observe little difference in costs between our arms, biasing analysis towards equivalence. While there is little that can be pre-emptively achieved, final analysis may present estimates of costs visually, in addition to descriptively, across this period to examine the effects (if any) of the COVID-19 pandemic on resource use and implications for RCT inference. We note that this would not apply to direct DAWBA or CAMHS appointment costs, and so supports their inclusion as a costing scenario.

7. Modelling

7.1 Lifecourse

While the receipt of any diagnosis of emotional difficulties in young people would likely lead to large divergences in lifecourse quality adjusted life years, the heterogeneity of conditions considered for diagnosis renders CUA modelling across the lifecourse infeasible. Secondary CEA is expected to be fully captured within the 12-month time horizon. We note that the trial was not funded for lifecourse modelling.

7.2 Future research

While not a designated outcome, the STADIA trial offers a wealth of data as the largest trial to administer multiple preference based HRQoL instruments concurrently in young people. Data from the trial may address current recommendations for research to test the face validity, practicality, internal consistency, and convergent validity of HRQoL of these instruments alongside other measures such as the SDQ, and concordance between adult proxy measures and child self-reported HRQoL (Furber & Segal, 2013).

8. Reporting/Publishing

8.1 Reporting standards

The final report of the trial will be submitted for peer review alongside a CHEERS checklist dependent on submission requirements (Husereau et al., 2013).

8.2 Reporting deviations from the HEAP

Any deviations from the HEAP will be reported in the first instance to the study team and disclosed alongside publication submissions as a supplementary note where deemed informative.

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10. Appendices

10.1 Example tables

Tables one through five present templates for reporting the data used within and the results from the economic evaluation.

Example Table 1. Within-trial intention-to-treat QALYs and costs: intervention vs TAU

Variable (*n*/N)	Mean Difference (95% CI)	
	Complete case	Multiple imputed
EQ-5D (/)		
Unadjusted		
Baseline adjusted		
EQ-VAS (/)		
Unadjusted		
Baseline adjusted		
EQ-5DY (/)		
Unadjusted		
Baseline adjusted		
CHU9D (/)		
Unadjusted		
Baseline adjusted		
Costs (/)		
NHS		
Societal		

EQ-5D, EuroQoL-5D. EQ-VAS, EuroQol Visual Analogue Score. Societal costs report the combination of NHS costs, participant or carer productivity losses, and out-of-pocket expenses. *n* corresponds to the number of univariate complete cases out of the sampled set size of N.

Example Table 2. Intervention/TAU summary statistics of intention-to-treat health economic data.

Variable	**Arm** (*n*=)					
	n	Mean	SD/95% CI	Min.	Median	Max.
Baseline						
EQ-5D						
EQ-VAS						
6 months						
EQ-5D						
EQ-VAS						
12 months						
EQ-5D						
EQ-VAS						
QALYs						
EQ-5D						
Unadjusted						
Baseline adjusted						
EQ-VAS						
Unadjusted						

Baseline adjusted	
Total costs (£)	
NHS	
Societal	

Data are mean (SD), or mean difference (95% CI). EQ-5D, EuroQoL-5D. EQ-VAS, EuroQol Visual Analogue Score.

Example Table 3. Self-reported healthcare service and resource use.

Service	TAU (*n*=)		Intervention (*n*=)	
	n/N	%	*n/N*	%
Any service use				
Inpatient				
General medical ward				
Acute psychiatric ward				
Outpatient				
A&E				
Radiology				
Physiotherapist				
Occupational therapist				
Psychiatrist				
Primary and community				
General practitioner				
GP home visit				
Practical nurse				
Psychologist				
Psychiatric Nurse				
Occupational Therapist				
Out-of-hours care				
Walk-in centre				
Social worker				
Private counselling or therapy				
Other use				

IP/OP/primary and community aggregate service use binary variables were amended to 1 or 0 if missing and participants specified individual service contact or no individual service use respectively. If binary variables declared no aggregate service use, individual service use binary variables were set to 0 if missing and no other individual service use was observed. Other use consisted of:

Example Table 4. Self-reported intensity of service use at point of access.

Service	TAU (*n*=)			Intervention (*n*=)		
Inpatient	*n/N*	Admissions	Bed days	*n/N*	Admissions	Bed days
General medical ward						
Acute psychiatric ward						
Outpatient		Visits			Visits	
A&E			-			-
Radiology			-			-
Physiotherapist			-			-
Occupational therapist			-			-
Psychiatrist			-			-
Primary and community		Contacts	Minutes		Contacts	Minutes
General practitioner						
GP home visit						
Practical nurse						
Psychologist						
Psychiatric Nurse						
Occupational Therapist						
Out-of-hours care						
Walk-in centre						
Social worker						

Data are mean (SD).

Example Table 5. Unit costs, productivity resources, and sources.

Service	Unit cost (£)	Source
Inpatient (per admittance)		
Non elective inpatient		
Outpatient (per visit)		
Accident and emergency		
Radiology		
Physiotherapist		
Occupational therapist		
Psychiatrist		
Primary and community (per contact minute)		
General practitioner		
GP home visit (excluding travel)		
Practical nurse		
Psychologist		
Psychiatric nurse		
Occupational therapist		
Social worker		
Out-of-hours care (per contact)		
Walk-in centre (per contact)		
Median team production multiplier		
Median weekly pay - gross (£)	**Male** **Female**	
Full-time		
Part-time		

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10.3 Technical note for researcher

An example and walk-through of the applied methods and STATA code may be found in the file location Shared\MHS\Medicine\NCTU\Health Economics ISDR\within-trial analysis and paper/FINAL ISDR HE Do file.do

It is recommended to build your own do file since the code is not designed to be run as a full unit, rather individual modules i.e. cleaning, then multiple imputation etc.

For the construction of CEACs, bootstrapped data will need exporting to an excel file. These bootstraps should then be used to construct INMB across a range of thresholds, then a cell at the bottom of each column created which measures the % of INMBs in the respective column that is >zero. This is the proportion cost effective which can be isolated and re-imported into STATA for graphing.