ORBIT Trial

Statistical and Health Economics Analysis Plan

1 Introduction

1.1 Purpose

This statistical analysis plan (SAP) contains details of the main statistical analyses for the ORBIT trial. These analyses are pre specified in order that they are not influenced by the collected trial data after unblinding. This SAP describes the statistical analysis of the clinical outcomes and the health economic analysis. It does not contain details of any qualitative analyses.

The SAP does not preclude the undertaking of further ad hoc or exploratory analyses, although the results of any such analyses should be interpreted with caution. Furthermore, the SAP does not preclude the adaptation of any part of the trial analysis should situations arise in which such adaptation is deemed necessary. Any such adaptation will be transparent and fully justified.

This SAP contains only a brief overview of the trial design, population, intervention, comparison and outcome variables. More detail can be found in the protocol version v3.0 dated 16 April 2018 which is stored on S:\Pop_Health\PCPH_Priment\Projects\Current\Non CTIMPS\ORBIT (Tourette)\6. Protocol\Final version.

1.2 Trial registration

The trial was prospectively registered with ISRTCN (ISRCTN70758207) and ClinicalTrials.gov (NCT03483493).

1.3 Authorship

The SAP has been written by Rebecca Jones (RJ), Louise Marston (LM), Marie Le Novere (MLN), Caroline Clarke (CC) and Rachael Hunter (RH).

Version 2.0

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2 List of Abbreviations

BNF	British National Formulary
C&A-GTS-QOL	Child and Adolescent Gilles de la Tourette Syndrome Quality of Life Scale
CA-SUS	Child and Adolescent Service Use Schedule
CACE	Complier average causal effect
CEAC	Cost effectiveness acceptability curve
CEP	Cost effectiveness plane
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impressions Scale
CHU9D	Child Health Utility 9D
CI	Confidence interval
CONSORT	Consolidated standards of reporting trials
DSMB	Data Safety and Monitoring Board
ICC	Intraclass correlation coefficient
ICER	Instrumental cost effectiveness ratio
MFQ	Mood and Feelings Questionnaire
ORBIT	Online remote behavioural intervention for tics
PSSRU	Personal Social Services Research Unit
PTQ	Parent Tic Questionnaire
QALY	Quality adjusted life year
SAP	Statistical analysis plan
SCAS	Spence Child Anxiety Scale
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
TTSS	Total Tic Severity Score
YGTSS	Yale Global Tic Severity Scale

3 Trial Summary

3.1 Title

Therapist guided, parent assisted, remote digital behavioural intervention for tics in children and adolescents with Tourette syndrome: an internal pilot study and single blind randomised controlled trial (ORBIT).

3.2 Aims

To provide evidence that, when compared with online education about tics, the online behavioural intervention will:

- Reduce the severity of tics in children and adolescents with Tourette syndrome.
- Improve impairment, functioning, behavioural and emotional difficulties, depression and anxiety symptoms and quality of life in children and adolescents with a tic disorder.
- Demonstrate cost effectiveness.

3.3 Population

Children and adolescents with Tourette syndrome or chronic tic disorder.

3.3.1 Inclusion criteria

Children and adolescents aged 9-17 years with Tourette syndrome or chronic tic disorder experiencing moderate or severe tics (assessed using the TTSS on the YGTSS), who access a PC/laptop/Mac users with broadband internet access.

3.3.2 Exclusion criteria

Children and adolescents are not eligible to participate if they have received a therapy for tics in the past 12 months, have changed (started or stopped) their tic medication within the last 2 months, have a diagnosis of alcohol/substance dependence, psychosis, suicidality, or anorexia nervosa or have a moderate or severe intellectual disability.

3.4 Intervention

Ten weeks of online, remotely delivered, therapist supported, exposure response prevention behavioural therapy for tics. The intervention may be delivered over a 12 week period in order to allow for periods of staff absence or patient holidays, but only 10 weeks of therapist time is provided.

3.5 Comparison

Ten weeks of online, remotely delivered, therapist supported, education about tics and co-occurring conditions.

3.6 Primary outcome

Total tic severity score (TTSS) on the Yale Global Scale (YGTSS) at three months post randomisation.

3.7 Design

A multi-centre, pragmatic, single blind, parallel group, randomised controlled trial with an internal pilot in children and adolescents with Tourette syndrome or chronic tic disorder to compare an online remote behavioural intervention for tics with online education.

3.8 Sample size

The required sample size for the trial (220 participants) has been calculated to have 90% power to detect an effect size of 0.5 standard deviations (SD) using a two-tailed, two-sample t-test (significance level of 0.05) comparing mean YGTSS TTSS at 3 months follow up for intervention and control trial arms, allowing for an estimated 20% loss to follow.

3.9 Randomisation

Participants will be randomly assigned in a 1:1 ratio to the online behavioural intervention or to online education. Randomisation will be stratified by centre (Nottingham and London), using block randomisation with varying block sizes. Full details can be found in the randomisation protocol.

3.10 Blinding

This is a single blind trial. Assessors are blind to treatment allocation; participants and therapists are not. Statisticians and health economists will also be blinded to allocation as far as possible until after the primary analysis has been agreed. However, the two stage analysis (see section 5.1) means that the 12 and 18 months data cannot be analysed blind to allocation. RJ will attend the Data Monitoring and Ethics Committee (DMEC) and may become unblinded as a result of this role if the committee requires any statistics to be reported separately by study arm.

4 Summary of Quantitative Trial Data

4.1 Observation times

Data will be collected at the following time points during the trial:

- Baseline
- Mid treatment (3 or 5 weeks post randomisation)
- Post treatment, the primary endpoint (3 months post randomisation)
- 6, 12 and 18 months post randomisation

Not all measures will be recorded at every time point. The data recorded at baseline and post intervention time points will constitute the full dataset for the purpose of analysis of the primary outcome. At each time point beyond baseline there is a data collection window. These are: + 7 days at the mid treatment time point; -2 weeks / +2 months at 3 months post randomisation; and -1 month / +2 months at 6, 12 and 18 months post randomisation. Data will be considered recorded at a given time point, provided that these data are collected from each participant within this window. Any participants for whom data are not collected within this time window will be considered missing at that follow up time for the purpose of the statistical analysis. The number and percentage of observations excluded for being outside the relevant time window will be summarised separately by study arm for the primary outcome only.

4.2 Outcome measures

4.2.1 Primary outcome

The primary outcome is tic severity at 3 months post randomisation as measured by the TTSS on the YGTSS.

4.2.2 Secondary outcomes

- Tic severity at other follow up time points (6, 12 and 18 months post randomisation) also measured by the YGTSS TTSS
- Tic related distress and impairment as measured by the YGTSS impairment scale
- Frequency and intensity of motor and vocal tics as measured by the Parent Tic Questionnaire (PTQ)
- Clinician determined symptoms as measured by the Clinical Global Impressions Scale (CGI)
- Psychological, social and academic functioning as measured by the Children's Global Assessment Scale (CGAS)
- Behavioural and emotional difficulties as measured by the Strengths and Difficulties Questionnaire (SDQ)
- Depressive symptoms as measured by the Mood and Feelings Questionnaire (MFQ)
- Anxiety symptoms as measured by the Spence Child Anxiety Scale (SCAS)
- Quality of life as measured by the Child Health Utility 9D (CHU9D) and the Child and Adolescent Gilles de la Tourette Syndrome Quality of Life Scale (C&A-GTS-QOL)
- Adverse events as measured by a modified version of the Hill and Taylor side effects scale

Further details on the scoring and ranges of all outcomes can be found in the trial protocol version v3.0 stored on S:\Pop_Health\PCPH_Priment\Projects\Current\Non CTIMPS\ORBIT (Tourette)\6. Protocol\Final version and the protocol paper[1]. Table 1 provides an overview of primary and secondary outcomes and the time points at which they will be collected.

Table 1: Data collection measures and time points

Measure	Baseline	Mid treatment (3 or 5 weeks)	3 months follow up (primary endpoint)	6, 12 and 18 months follow up
Primary outcome				
Tic severity (YGTSS TTSS)	✓		✓	✓
Secondary outcomes				
Impairment (YGTSS)	✓		✓	✓
Tic frequency and intensity (PTQ)	✓	✓	✓	✓
Symptom improvement (CGI)			✓	✓
Functioning (CGAS)	✓		✓	✓
Behavioural and emotional difficulties (SDQ)	✓		✓	✓
Depression symptoms (MFQ)	✓	✓	✓	✓
Anxiety symptoms (SCAS)	✓		✓	✓
Quality of life (CHU9D)	✓		✓	✓
Tourette Syndrome specific quality of life (C&A-GTS-QOL)	✓		✓	
Serious adverse events	✓	✓	✓	✓ *
Other measures				
Treatment credibility		✓		
Treatment satisfaction			✓	
Need for further treatment			✓	
Concomitant interventions	✓		✓	✓

*Notes: * Serious adverse events are collected at 6 months post randomisation only (ie, not at 12 and 18 months).*

4.3 Other available data

Demographic characteristics of the participants will be collected at baseline in order to assess the balance between the study arms. This information will include:

- Date of birth (age)
- Gender
- Ethnicity
- Parental education
- Parental occupation
- Child or adolescent's current diagnoses
- Child or adolescent's current interventions and medications

Other available data will comprise:

- Centre identifier
- Dates of assessments
- Whether the child or adolescent met the therapist
- Treatment completion, defined as completion of the first four child chapters of the intervention
- Treatment credibility
- Treatment satisfaction and need for further treatment
- Concomitant treatments and medications
- Reasons for withdrawal or loss to follow-up (if supplied)

5 Statistical Analyses of Clinical Outcomes

5.1 Organisation of data and analyses

The trial comprises two distinct phases: phase 1 is a controlled effectiveness evaluation; phase 2 addresses long term maintenance of effects. Phase 1 follows participants up at 3 (primary endpoint) and 6 months, maintaining randomisation. After 6 months participants may freely change or start medication or new therapy for their tics. Phase 2 is a naturalistic follow up at 12 and 18 months. Scientifically these two phases address different questions and will therefore be analysed and reported separately.

Trial analyses will accordingly be performed in two stages: (1) data collected at mid treatment and at 3 and 6 months follow up will be analysed after collection of the 6 month data from the last participant to be randomised; (2) data collected at 12 and 18 month follow up will be analysed after the last data has been collected from the 18 month time point. This two stage analysis will require two database locks. The analysis of the primary outcome will be carried out in stage 1. All measures to be analysed at stage 2 are secondary outcomes.

Data will be unblinded for statisticians and health economists at stage 1 after the primary analysis has been completed and confirmed. It will not be possible for data from the 12 and 18 month follow up time points to be analysed blind to allocation. However, participants and all other blinded members of the study (including outcome assessors) will remain blind to arm allocation throughout phase 2 of the trial.

The SAP will be finalised and approved prior to unblinding. The programs and code to be used for statistical analyses will be prepared prior to unblinding as far as possible. Two statisticians will perform the analysis relating to the primary outcome independently, in order to ensure its accuracy.

Prior to performing analyses, basic checks will be performed by the statisticians on the blinded data to ensure accuracy. Each outcome (primary and secondary) variable and baseline demographic variable will be checked for:

- Missing values
- Values outside an acceptable range
- Other inconsistencies

If missing values or other inconsistencies are found, the corresponding data will be sent to the Trial Manager for checking and will either be corrected or deemed to be missing, as appropriate.

5.2 Interim analyses

Baseline demographic characteristics will be summarised for the sample as a whole for the DSMB. Primary and secondary outcomes at baseline and the primary endpoint (3 months post randomisation) will likewise be summarised for the whole sample.

5.3 Recruitment and retention

A CONSORT diagram will be presented to provide a detailed description of participant numbers at each time point during the trial. In addition, a table summarising the number of participants who have been lost to follow up at each stage of the trial and reasons for loss to follow up (if supplied) will be presented.

5.4 Description of demographic variables at baseline

The demographic information collected at baseline will be presented in a table summarised separately by study arm. Categorical variables will be reported as counts and percentages. Continuous variables will be summarised as means and standard deviations (SD) or medians and interquartile ranges as appropriate depending on the distribution of the data. No statistical tests will be performed to assess baseline differences between study arms.

5.5 Primary outcome analysis

The primary outcome is the YGTSS TTSS. The primary end point is 3 months post randomisation. The primary analysis will be based on available data and conducted according to the intention to treat principle. The mean difference in the primary outcome in the intervention arm compared with the control arm will be estimated from a linear regression model with YGTSS TTSS at 3 months post randomisation as the outcome and study arm as the main explanatory variable, adjusting for the baseline measure of the YGTSS TTSS and for centre (Nottingham or London), as used for stratified randomisation.

The estimated treatment effect will be reported with accompanying 95% confidence interval (CI) and p value.

5.5.1 Model checking

The statistical model for the primary outcome analysis includes an assumption that the residuals are normally distributed. This assumption will be checked through the construction of appropriate histograms and normal quantile plots. If these plots suggest that residuals are not normally distributed, then appropriate transformations of the primary outcome or application of the bootstrap method will be considered.

5.5.2 Missing data

Bias due to missing data will be investigated by comparing the baseline characteristics of participants with and without missing values. Depending on the quantity of missing values, the predictors of missingness will be identified. We will then perform a sensitivity analysis by including any predictors of missingness as explanatory variables in the primary outcome model, in order to restore the missing at random assumption. Multiple imputation will not be performed, since it offers few advantages for missing outcome data[2].

The primary analyses will be a complete case analysis. Analyses investigating the impact of missing data will be considered supportive.

5.6 Secondary analyses

Secondary outcomes are listed above and comprise tic severity (the primary outcome) at 6, 12 and 18 months post randomisation, all secondary outcome measures at 3, 6, 12 and 18 months post randomisation and PTQ and MFQ at the mid treatment time point.

In the stage 1 analysis, the effect of the intervention on secondary outcomes will be estimated using separate linear regression models for each outcome at each follow up time point (mid treatment, 3 and 6 months), with study arm as the main explanatory variable and adjusting for the baseline measure of the outcome and centre.

In the stage 2 analysis, one linear mixed model will be fitted for each secondary outcome, with measures from all available time points (mid treatment, 3, 6, 12 and 18 months) as the outcome and a random effect of participant to account for correlations between the repeated measures on each individual over time. The main explanatory variables will be specified as treatment, time and the treatment by time interaction, adjusting for the baseline measures of the outcome and centre. The effect of the intervention on secondary outcomes at 12 and 18 months will be estimated from this model. Estimated effects will be reported with 95% confidence intervals. P values will not be reported for secondary analyses.

In addition to the above analyses, a sensitivity analysis will be performed for the YGTSS TTSS only to account for the fact that after 6 months participants are permitted to change or start medication or new therapy for their tics. This analysis will use the same linear mixed model method described above, but will adjust additionally for change in medication and/or other therapy. This analysis will only be performed if a sufficient number of participants change medication and/or therapy for the results to be meaningful.

Non normally distributed continuous outcomes will be analysed using the bootstrap method and bias corrected 95% CI will be reported.

These analyses will be considered exploratory and secondary outcomes will be analysed using available data only.

5.7 Subgroup analyses

No subgroup analyses are planned.

5.8 Adverse events

The number, nature and severity of serious adverse events (if any) will be reported separately by study arm at each follow up time point. The number of participants who experience adverse events will likewise be reported separately by study arm.

5.9 Agreement

YGTSS raters will undergo an initial training phase designed to enable them to reach agreement with the trial's expert rater. Subsequent testing phases, repeated every six months, will collect data to assess the extent to which raters agree with the expert rater.

Results of this assessment will be reported as the number and percentage of raters whose scores are within 15% of the expert rater's score at each time point. These results will be descriptive only.

5.10 Reporting

Analyses will be reported with regard to the CONSORT checklist[3] and with any particular requirements of academic journals and the funders to which the results of analyses are submitted.

6 Health Economic Analyses

6.1 Aims

6.1.1 Stage 1 analysis

The primary aim of the stage 1 health economic analysis is to calculate the mean incremental cost per point difference in TTSS on the YGTSS of the online behavioural intervention compared to online education at 6 months from a health and social care cost perspective.

Secondary aims are to:

- Calculate the mean incremental cost per point difference in TTSS on the YGTSS at 6 months from a wider cost perspective.
- Calculate the mean incremental cost per quality adjusted life year (QALY) gained calculated using the CHU9D over 6 months from a health and social care cost perspective.
- Calculate the mean incremental cost per QALY gained over 6 months from a wider cost perspective.

6.1.2 Stage 2 analysis

The primary aim of the stage 2 analysis will be to calculate the mean incremental cost per point difference in TTSS on the YGTSS of the online behavioural intervention compared to online education from a health and social care cost perspective at 18 months following the naturalistic follow up.

As detailed above, after 6 months participants are permitted to change or start medication or new therapy for their tics. This 18 month analysis will include adjustment for change in medication and/or other therapy after 6 months, in line with section 5.6 above.

Secondary aims are the same as for the stage 1 analysis but with an 18 month time frame, discounting at 3.5% annually for both costs and effects.

- Calculate the mean incremental cost per point difference in TTSS on the YGTSS at 18 months from a health and social care cost perspective.
- Calculate the mean incremental cost per point difference in TTSS on the YGTSS at 18 months from a wider cost perspective.
- Calculate the mean incremental cost per quality adjusted life year (QALY) gained calculated using the CHU9D over 18 months from a health and social care cost perspective.
- Calculate the mean incremental cost per QALY gained over 18 months from a wider cost perspective.

6.1.3 Economic model

A decision model will aim to calculate the incremental cost per QALY gained over a 10-year time horizon from a health and social care cost perspective. This will be covered in a subsequent analysis plan covering only the decision model.

6.2 Outcomes

The YGTSS and CHU9D have been described above (see section 4). The CHU9D is completed by the parent and the child at each time point.

Resource use will collected using a modified version of the Child and Adolescent Service Use Schedule (CA-SUS) with a particular focus on other services that child may use in relation to treatment for tics outside of the remotely delivered therapist support in the intervention arm. It also asks about other community and secondary health care services, days missed from school, additional educational support, voluntary services, out of pocket costs, medications, nutritional supplements and other complimentary medications. This will be completed by parents at baseline, 3,6, 12 and 18 months post randomisation.

6.3 Cost data

6.3.1 Resource Use

Descriptive statistics for the percentage of patients using a type of contact, and mean number of contacts, for each type of health and social care collected by the CA-SUS will be

reported at baseline, 3, 6, 12 and 18 months. Information on data completeness will also be reported.

6.3.2 Cost of remotely delivered therapist support

Information collected on therapist time spent delivering remote therapist support multiplied by the cost of the therapist for each child will be used to calculate the patient-level cost per child. The mean cost per child and standard deviation will be reported for each arm. The range of mean times spent per child and cost per child by centre and arm will also be reported.

We will also include information on the cost of ongoing maintenance and support for the website. The cost to develop the website will not be included as it is considered a sunk cost. We will collect information to estimate the cost of implementation (changes required to services including staff training and IT infrastructure) that may be needed to implement the intervention. This will be divided by the number of children in the trial as the upper estimate of the cost per child for the intervention. Dividing by the maximum number of children this could be provided to, based on information on the prevalence of tics and assumed uptake throughout England, will be used to provide a lower estimate.

6.3.3 Cost of health and social care resource use

The cost of acute and community health and social care service use for the online behavioural intervention versus treatment as usual will be calculated, using a modified parent-completed version of the Child and Adolescent Service Use Schedule (CA-SUS).

These will be costed for each child using unit costs from the most recent Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU)[4] and reference costs. Medication, nutritional supplements and other complimentary medications will be costed from the British National Formulary (BNF) and online sources such as Boots when not available from the BNF.

Mean cost per patient for the remote digital intervention versus treatment as usual will be reported as total cost per child and by type of service use with particular focus on tic related service use at 6 months.

Difference in health and social care costs between the online behavioural intervention and online education will be reported. Costs will be adjusted by baseline values and centre using regression analysis. A bias corrected bootstrap method will be used to calculate 95% CIs. This will be done at 6 and 18 months, as described above.

6.3.4 Wider costs

Wider costs, also collected via the CA-SUS, include the cost of educational support, out-of-pocket costs and the cost of days off school due to Tourette syndrome. Educational support will be costed using published sources. Out-of-pocket costs will be included as the value entered by parents on the CA-SUS. Costs of days off will be costed using a human capital

approach by multiplying the number of days off school by the daily wage of the caregiver required to take a day off work to look after the child.

Difference in wider costs between the online behavioural intervention and online education will be reported. Costs will be adjusted by baseline values and centre using regression analysis. A bias corrected bootstrap method will be used to calculate 95% CIs. This will be done at 6 and 18 months, as described above.

6.4 Quality of life

The primary measure used to calculate QALYs will be the parent completed CHU9D. QALYs will be calculated as the area under the curve using the CHU9D utility values at baseline, 3, 6, 12 and 18 months and by applying the algorithm developed by Stevens[5] at each time point. For online behavioural intervention versus online education, mean utility values at each time point, mean unadjusted QALYs from baseline to 6 and 18 months, and mean QALYs adjusting for baseline and centre using regression analysis will be reported. A bias corrected bootstrap method will be used to calculate 95% CIs.

A secondary analysis will use child-completed CHU9D responses and the method above to calculate QALYs.

6.5 Discounting

No discounting will be included in the first stage analysis as the results are for a time horizon of less than a year. In the second stage analysis all costs and QALYs that occur between 12 and 18 months will be discounted at a rate of 3.5% in line with NICE guidance[6].

6.6 6 month within trial analysis

The stage 1 economic evaluation will be a within trial analysis over 6 months.

6.6.1 Incremental cost-effectiveness ratio (ICER)

We will report the mean incremental cost per point difference between groups on the YGTSS estimated as specified in section 5.6, at 6 months. Costs will be bootstrap adjusted costs as specified in sections 6.3.2 and 6.3.3 and will include the cost of the online behavioural intervention and the cost of health and social care services respectively. Costs will be discounted as specified in section 6.5.

6.6.2 Cost effectiveness acceptability curve (CEAC) and Cost effectiveness plane (CEP)

Means and 95% CIs for the YGTSS and costs will be based on bootstrapped results and these will be used to calculate the probability that the online behavioural intervention is cost effective compared to online education for a range of values of willingness to pay for a 1 point difference in YGTSS. A cost effectiveness plane illustrating the bootstrapped results will also be reported.

6.7 Missing data

Missing data will be accounted as specified in section 5.5.2 above.

6.8 Sensitivity analyses

We will test the impact on the results of using a range of assumptions and values used to inform the costing of the intervention described in 6.3.2.

6.9 Secondary within trial analyses

ICERs, CEACs and CEPs will be reported for the following analyses:

- Wider cost perspective and difference in YGTSS at 6 months.
- Health and social care cost perspective and QALYs over 6 months based on the parent completed CHU9D.
- Wider cost perspective and QALYs over 6 months based on the parent completed CHU9D.
- Health and social care cost perspective and QALYs over 6 months based on the child completed CHU9D.
- Wider cost perspective and QALYs over 6 months based on the child completed CHU9D.

6.10 18 month naturalistic analysis

The 18 month naturalistic analysis will follow the same analysis plan as the 6 month within trial analysis as detailed in sections 6.6.1 to 6.9 but with an end point of 18 months. Sensitivity analysis will include adjusting for whether participants have chosen to change / start medication or a new therapy for their tics once allowed after the first 6 months.

7 References

1. Hall CL, Davies EB, Andrén P, et al. Investigating a therapist-guided, parent-assisted remote digital behavioural intervention for tics in children and adolescents—'Online Remote Behavioural Intervention for Tics' (ORBIT) trial: protocol of an internal pilot study and single-blind randomised controlled trial. *BMJ Open* 2019;9(1):e027583. doi: 10.1136/bmjopen-2018-027583

2. Sullivan TR, White IR, Salter AB, et al. Should multiple imputation be the method of choice for handling missing data in randomized trials? *Stat Methods Med Res* 2018;27(9):2610-26. doi: 10.1177/0962280216683570 [published Online First: 12/19]

3. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332. doi: 10.1136/bmj.c332

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5. Stevens K. Assessing the performance of a new generic measure of health-related quality of life for children and refining it for use in health state valuation. *Applied Health Economics and Health Policy* 2011;9(3):157-69. doi: 10.2165/11587350-000000000-00000

6. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 2018.