

Health Economic Analysis Plan for Actissist 2.0: Active Assistance for Psychological Therapy 2.0 (Actissist 2.0): Digital Intervention for Co-producing care in psychosis.

Version: v0

Roles and responsibilities:

Name	Role
Emma McManus, Research Fellow University of Manchester	Health Economist conducting analysis
Luke Munford, Senior Lecturer University of Manchester	Health Economist providing oversight

Source of funding:

The trial was funded by the Medical Research Council (project number MR/P026664/1).
Study registration: ISRCTN76986679.

Emma McManus and Luke Munford have received no funding for the health economic analysis.

Abbreviations:

CBT: Cognitive Behavioural Therapy

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

HEAP: Health Economics Analysis Plan

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

PANSS: Positive and Negative Syndrome Scale

PSS: Personal and Social Services

QALY: Quality-Adjusted Life Year

SUR: Seemingly Unrelated Regression

TAU: Treatment as Usual

Purpose of HEAP:

This document will provide details of the health economic analysis to be conducted using data collected as part of the Actissist2 study. The Actissist2 study was a clinical trial conducted from March 2018 to June 2020. Whilst health resource use and outcomes were collected at the time of the trial, the economic analysis was not started until 2024. The contents of this HEAP follow the guidelines presented in Thorn et al. [1].

Overview of the clinical trial:

The Actissist2 study was a two-arm trial where participants were randomised to either receive: the Actissist app in addition to treatment as usual (TAU) or the ClinTouch symptom-monitoring app (control arm) plus TAU. Actissist is a smartphone app that delivers cognitive behavioural therapy (CBT)-informed strategies in the flow of daily life. ClinTouch is a symptom-monitoring app that triggers, collects and wirelessly uploads symptom data to a server.

Participants were recruited between March 2018 and December 2019 and were eligible to be included in the trial if they:

- were aged over 16 years,
- met the diagnosis criteria for schizophrenia-spectrum diagnosis,
- were in contact with mental health services within five years from onset of first psychotic episode,
- met a criterion level of positive symptoms severity, indicated by a score of >3 (symptom present) on any PANSS positive item and a score of >3 (symptom present) on any PANSS negative or PANSS general items,
- were English speaking,
- were able to provide informed consent,
- were not currently participating in another trial.

The planned sample size of the trial was 170 participants, with a 1:1 randomisation stratified by service. The primary outcome was the total score from the Positive and Negative Syndrome Scale (PANSS), measured at 12 weeks.

The full clinical trial protocol can be found at [2] and the clinical results are published in Bucci et al. [3].

Health Economic Evaluation

Aim of health economic analysis:

The economic evaluation aims to assess the short-term cost-effectiveness of the Actissist app compared to the ClinTouch symptom-monitoring app for individuals with a diagnosis of schizophrenia.

Overview of planned analysis:

A cost-utility analysis will be undertaken from the NHS and personal social service (PSS) perspective as recommended by the National Institute for Health and Care Excellence (NICE) [4].

Jurisdiction and Perspective:

The Actissist2 clinical trial was conducted in England, which has a National Health Service (NHS). As such, the economic evaluation will be conducted from the perspective of the NHS and personal social services (PSS).

Time horizon:

The time horizon of the economic evaluation will follow that of the clinical trial, 6 months.

Statistical software:

All statistical analyses will be conducted in STATA 16, with some elements of costing conducted in Microsoft Excel.

Identification / measurement / valuation of resources:

A healthcare resource use questionnaire was used to identify resource use. This was completed by participants at baseline, 12 weeks and 24 weeks. An example of the health resource use questionnaire used is provided in Appendix 1 of this document.

All resource use will be valued in monetary terms using appropriate UK unit costs (such as the PSSRU [5] or Prescription Cost Analysis [6]), using a standard price year for the time that the data was collected (price year 2020/21). Where additional assumptions are required in order to generate a unit cost, these will be thoroughly reported.

Identification / measurement / valuation of outcomes:

The primary outcome measure of this economic evaluation will be Quality-Adjusted Life Years (QALYs), generated from utility scores derived from the EQ-5D-5L [7]. Participants completed the EQ-5D-5L at baseline, 12 weeks and 24 weeks. The EQ-5D-5L will be valued using published tariffs for the UK to generate utility scores. Currently, NICE recommend using the Crosswalk value set [8] to generate such utility values [9]. QALYs will then be calculated using the time spent in each health state using the date individuals completed the EQ-5D-5L questionnaire and area under the curve calculations. Following Hunter et al., we calculated the QALYs at the individual level (rather than at the group level) [10].

Analysis population:

This economic evaluation will be conducted on complete cases, that is, all randomised participants who have responses recorded at all three time points: baseline, 12 weeks and 24 weeks. We will assume that individuals randomised to each of the trial arms, received that treatment, following the 'intention to treat' principle.

Discount rates for costs and benefits:

It is not necessary to discount costs or benefits given the short time-horizon of the analysis (6 months).

Cost effectiveness thresholds:

Conventional cost-effectiveness thresholds of NICE will be considered, which are currently: a willingness to pay per additional QALY generated of between £20,000 to £30,000.

Statistical decision rules:

Mean differences in costs, QALYs and net benefits between the two trial arms will be estimated with associated 95% confidence intervals.

Analysis of resource use:

Differences in the use of services between the two trial arms will be described and compared.

Analysis of costs

Intervention costs:

Both arms of the trial required the supply of a mobile smartphone (for those who did not own one), the payment of a phone contract for the duration of the trial (3 months) and time with a

nurse or researcher to show individuals how to use the apps, referred to as 'onboarding'. Given that these costs were encountered in both trial arms, they will not be considered in the main analysis. Instead, a theoretical cost of Actissist in addition to TAU will be considered in a sensitivity analysis.

Healthcare costs:

Within-trial total costs for each patient will be calculated from the sum of all costs (totalling primary, secondary and community care services, and medication use). Differences in overall mean costs will then be compared between trial arms. Baseline costs, relating to the 6-months preceding randomisation will be used to adjust for any baseline imbalances in subsequent regression analyses.

Analysis of outcomes:

The mean QALYs generated per trial arm will be compared. Baseline utility values will be controlled for in subsequent regression analyses.

Blinding:

The health economist will be blinded as much as possible during the analysis. They will be blinded when applying unit costs and calculating quality of life outcomes. However, for the final part of the analysis, the health economist will need to become unblinded to allocation group in order to perform the analyses.

Data cleaning rules:

Data cleaning has been carried out as part of the clinical trial, during the data collection and entry period. If subsequent implausible values are suspected, these will be discussed with a clinical specialist, who can advise if the reported value is clinically likely. This may be relevant when costing medications, particularly the classification of depot injections or oral medications and the daily dosages reported. All assumptions made with regards to data cleaning will be reported within the final analysis.

Missing data:

The economic evaluation will consider only complete cases, and therefore will include only participants who have resource use and EQ-5D-5L responses recorded for baseline, 12 weeks and 24 weeks, as well as the date for when these responses were collected. Where a resource is not recorded, it will be assumed that this is because an individual did not use that resource during the recall period.

Analysis of cost-effectiveness:

Cost and QALY data will be combined to calculate an incremental cost-effectiveness ratio (ICER) from the NHS and PSS perspective. This will involve using a Seemingly Unrelated Regression (SUR) model, which will account for the correlation between costs and QALYS. The regression model will adjust for baseline costs and utility scores, as well as other sociodemographic factors.

Sampling uncertainty:

Nonparametric bootstrapping will be used to determine the level of sampling uncertainty surrounding the mean ICER by generating 10,000 estimates of incremental costs and benefits.

Subgroup analyses or analysis of heterogeneity:

There are no planned subgroup analyses for the economic evaluation.

Sensitivity analyses:

Two sensitivity analyses are planned. Firstly, if there is a sizeable number of respondents for whom there is not a date of assessment recorded but where other information is recorded, we will repeat the main analysis, but assume that individuals have been followed up at exactly 12 and 24 weeks respectively so that a greater number can be included in the analysis sample.

Secondly, we will also conduct analyses where we will attribute costs to delivering the Actissist intervention. This will reflect the real-world costs that would be associated with rolling out the intervention (given that it is not routine practice to deliver ClinTouch). These intervention costs will include the provision of mobile phones for individuals without a smart phone, contract payment and app on-boarding time. We will consider these in three stages, firstly just considering the cost of the hour on boarding, secondly considering the onboarding and phone loan for the percentage of individuals who reported not owning a smart phone and lastly, considering these costs in addition to the phone contract costs. These analyses however will likely represent a lower bound of Actissist's cost-effectiveness, given that all of the possible intervention costs are considered, but the potential effectiveness of ClinTouch over and above treatment as usual are not considered, which therefore may underestimate the potential cost-effectiveness of Actissist.

Reporting standards:

Results of the economic evaluation will be written up and submitted to a peer-reviewed journal. Reporting will follow the criteria described in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [11].

Deviations from the HEAP:

Where there are any deviations from the analysis proposed in this document, these will be clearly described and highlighted in the resulting manuscript.

Health economic collection tools:

An example of the health resource use questionnaire used in the clinical trial is provided in Appendix 1 of this document. Health outcome measures (EQ-5D-5L) were collected using the licensed materials provided by EuroQol.

References

1. Thorn, J.C., et al., *Content of Health Economics Analysis Plans (HEAPs) for trial-based economic evaluations: expert Delphi consensus survey*. *Value in Health*, 2021. **24**(4): p. 539-547.
2. Actissist Trial. *Actissist*. 2024 [cited 2024 22nd November]; Available from: <https://sites.manchester.ac.uk/actissist/>.
3. Bucci, S., et al., *Effects of Actissist, a digital health intervention for early psychosis: A randomized clinical trial*. *Psychiatry Research*, 2024: p. 116025.
4. National Institute for Health and Care Excellence. *NICE health technology evaluations: the manual 2023* [cited 2023 31st October]; Available from: <https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation-2>.
5. Personal Social Services Research Unit. *Unit Costs of Health and Social Care programme (2022 – 2027)*. 2024 [cited 2024 18th November]; Available from: <https://www.pssru.ac.uk/unitcostsreport/>.
6. NHS Business Services Authority. *Prescription Cost Analysis - England*. 2024 [cited 2024 18th November]; Available from: <https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis-england>.
7. EuroQol. *EQ-5D-5L User Guide*. 2024 [cited 2024 19th November]; Available from: <https://euroqol.org/publications/user-guides>.
8. Van Hout, B., et al., *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets*. *Value in health*, 2012. **15**(5): p. 708-715.
9. National Institute for Health and Care Excellence. *Position statement on use of the EQ-5D-5L value set for England (updated October 2019)*. 2019 [cited 2024 19th November]; Available from: <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l>.
10. Hunter, R.M., et al., *An educational review of the statistical issues in analysing utility data for cost-utility analysis*. *Pharmacoeconomics*, 2015. **33**: p. 355-366.
11. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations*. *MDM Policy & Practice*, 2022. **7**(1): p. 23814683211061097.

[Resource Use Questionnaire – continued]

2. Use of hospital outpatient appointments

Please tell us about any planned hospital outpatient appointments (lasting 4 hours or less) in the last **6 months** (*please do not include any hospital inpatient admissions, day hospital appointments or accident and emergency services here, we ask you for information about these questions in 1, 3 and 4*).

If you have not used a service please enter '0'. If you don't know whether you have used a service, then please tick the '**Don't know**' box. Thank you.

A. Have you attended any hospital outpatient appointments which lasted for **4 hours or less** during the last 6 months?

No Yes Don't know

If YES, please tell us about the department or speciality and the number of appointments which **lasted 4 hours or less**. If you don't know the details asked for, then please tell us as much as you can and also tick the '**Don't know**' box (to help us analyse the data). Thank you.

Department or speciality or reason for using the service	Total number of visits during the last 6 months	Total number of visits in the last month	Don't know
Please list each admission and number of days separately			

[Resource Use Questionnaire – continued]

3. Use of day hospital appointments

Please tell us about any planned day hospital appointments (lasting more than 4 hours but not overnight) in the last **6 months** (*please do not include any hospital inpatient or outpatient hospital appointments or accident and emergency services here, we ask you for information about these in questions 1, 2 and 4*).

If you have not used a service please enter '0'. If you don't know whether you have used a service, then please tick the '**Don't know**' box. Thank you.

A. Have you attended any day hospital appointments which lasted for more than 4 hours (but not overnight) during the last 6 months?

No Yes Don't know

If YES, tell us about the department or speciality and the number of appointments **more than 4 hours (but not overnight)**. If you don't know all the details asked for, then please tell us as much as you can and also tick the '**Don't know**' box (to help us analyse the data). Thank you.

Department or speciality or reason for using the service (e.g. minor surgery, occupational therapy, assessment of mental health problems, acute mental health treatment)	Total number of visits during the last 6 months	Total number of visits in the last month	Don't know
Please list each type of department/clinic or speciality or reason for using the service separately and tell us the number of visits for this department/clinic or speciality			

[Resource Use Questionnaire – continued]

4. Use of accident and emergency (A&E) services

Please tell us about any accident and emergency (A&E) services in the **last 6 months** (please do not include any hospital inpatient admissions, outpatient or day hospital appointments here, we ask you for information about these in questions 1, 2 and 3).

If you have not used a service please enter '0'. If you don't know whether you have used a service, then please tick the '**Don't know**' box. Thank you.

A. Have you attended an Accident and Emergency (A&E) unit during the last **6 months**?

No Yes Don't know

B. Please tell us about the number of A&E visits you had which did **NOT** lead to a hospital admission.

Accident and Emergency visits not leading to inpatient admission	
Total number of visits during the last 6 months	Total number of visits during the last month?

C. Were you admitted into a hospital as an inpatient directly from the Accident and Emergency (A&E) unit during the last **6 months**?

No Yes Don't know

D. Please tell us about the number of A&E visits you had which **did lead** to a hospital admission. Please tell us about the Accident and Emergency visit in the table below and put details for the inpatient stay in the table in question 1. Thank you.

Accident and Emergency visits leading to inpatient admission	
Total number of visits during the last 6 months	Total number of visits during the last month?

[Resource Use Questionnaire – continued]

5a. Use of primary and community based health services

Please tell us whether and how much you have used any of the following services in the last **6 months**. If you have not used a service please enter '0'. If you don't know whether you have used a service, then please tick the '**Don't know**' box. Thank you.

GP practice services	Total visits in the last 6 months	Total visits in the last month	Don't know
GP (at the surgery/practice)			
GP (at your home)			
Practice Nurse (at the surgery)			
Nurse (at your home)			

Other physical care services (e.g. minor illness or injury, diagnostic test, blood sample)	Total visits in the last 6 months	Total visits in the last month	Don't know
Walk in centre			
Blood test			
Other (please specify)			

5b. Use of primary and community based health services cont.

Please tell us whether and how much you have used any of the following services in the last **6 months**. If you have not used a service please enter '0'. If you don't know whether you have used a service, then please tick the '**Don't know**' box. Thank you.

Mental health services	Total visits in the last 6 months	Total visits in the last month	Don't know
Community mental health team worker (please specify)			
Community mental health team meeting			
Crisis team/emergency service			
Psychiatrist			
Other (please specify)			
Other (please specify)			

[Resource Use Questionnaire – continued]

5c. Use of primary and community based health services cont.

Please tell us whether and how much you have used any of the following services in the last **6 months**. If you have not used a service please enter '0'. If you don't know whether you have used a service, then please tick the '**Don't know**' box. Thank you.

Other social support services (e.g. social worker, home help, care worker, occupational or physiotherapist) (please specify)	Total visits in the last 6 months	Total visits in the last month	Don't know

6a. Extra costs

Please tell us whether you have had any extra costs (over and above your normal expenditure) in the last **6 months**. If you have not had an extra cost please enter '0'. If you don't know whether you have had any extra costs, then please tick the '**Don't know**' box. Thank you.

	Amount spent (in last 6 months, £)	Don't know
Prescribed, and over-the-counter, medications		
Travel costs (e.g. parking fees for any hospital, GP or day-care)		
Private health care (include use of alternative therapies and practitioners)		

6b. During the last 6 months, are there any other MAJOR (£50+) one-off expenses that you have had to meet?

No Yes Don't know

[Resource Use Questionnaire – continued]

Description of major one off expense	Amount spent in the last 6 months	Was this related to your mental health?	Don't know
Please list each type of expense separately			