RAPID Health Economic Analysis Plan

Trial: Remote Approaches to Psychosocial Intervention Delivery (RAPID) trial: a multi-arm, multi-stage randomised controlled trial

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Roles and responsibilities

This HEAP was prepared by Gemma Shields. The trial health economists are responsible for conducting and reporting the economic evaluation in accordance with the HEAP. A Research Associate will be recruited to work on the analysis with the support of the health economics lead. The HEAP has been independently reviewed by three health economists external to the project (Anju Keetharuth, University of Sheffield, Elizabeth Camacho, University of Liverpool and Linda Davies, University of Manchester).

Contents

Abbreviations

AHS	Adult HOPE Scale
CEA	Cost-effectiveness Analysis
CEAC	Cost-effectiveness Acceptability Curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHU-9D	Child Health Utility 9D Index
CSSRS	Columbia-Suicide Severity Rating Scale
CUA	Cost-utility Analysis
DSU	Decision Support Unit
EPQ	Economic Patient Questionnaire
EUPD	Emotionally Unstable Personality Disorder
HEAP	Health Economics Analysis Plan
ICER	Incremental Cost-effectiveness Ratio
INBRA	Incremental Net-benefit Regression Analysis
ITT	Intention-to-treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NMB	Net Monetary Benefit
NS-SEC	National Statistics Socio-economic
PHA	Psychiatric hospital admissions
PPI	Patient and Public Involvement
PRQ	Process of Recovery Questionnaire
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
ReQoL-10	Recovering Quality of Life – 10 item version12
ReQoL-UI	Recovering Quality of Life – Utility Index
SMHP	Serious Mental Health Problems
SUI	Service-Use Interview
TAU	Treatment as Usual

UK	United Kingdom
WTP	Willingness-to-pay

Trial overview

The following sections reproduce and summarise key details from the research proposal and the RAPID trial protocol.[1]

Trial background

Severe mental health problems (SMHPs) encompass diagnoses such as psychosis, bipolar and personality disorders. People with SMHPs face higher rates of premature mortality, co-morbid physical and mental health problems, cognitive impairment, social exclusion, treatment side effects and reduced opportunities related to employment and education.[2–7] Further, carers of people with SMHP face reduced quality of life, physical health, employment rates and increased financial burden.[8]

The cost of mental ill-health in the UK is substantial: a report estimated that in 2022 the economic and social costs of mental ill-health amounted to £300 billion, including £60 billion in healthcare costs, £110 billion in economics costs (e.g. productivity losses) and £130 billion in human costs (i.e. health losses expressed in monetary terms).[9] Although hospital admissions due to psychiatric hospital admissions (PHAs) are decreasing (by 28.4% from 1998/99 to 2019/20) the burden is significant.[10] PHAs are associated with a significant burden placed on the affected individual, including stigma, loss of relationships, employment and housing, and traumatisation.[11,12] PHAs are the most expensive form of mental health care with the estimated costs of involuntary psychiatric admissions in the UK totalling £6.8 billion over an 8-year period (2008/9 to 2015/16).[13] Esposti et al. found that schizophrenia accounted for almost half of psychiatric bed days.[10]

Crisis teams provide community care to people with SMHPs who are experiencing a suicidal crisis.[14] However, over half of the crisis team patients have an admission within a year of discharge from hospital.[15] People with an SMHP diagnosis are the diagnostic groups most likely to have an admission following a crisis team contact and the majority of first admissions are due to suicidality.[16,17] Interventions designed to reduce suicidal ideation may have an effect on reducing PHAs given the majority of first admissions occur in response to a suicidal crisis.[17] Suicidal ideation is common in people with SMHPs.[18,19] Digital interventions have been proposed to improve access to treatment for people who are at risk of suicide and have the potential to extend the scalability and accessibility of an intervention.[20]

The Remote Approaches to Psychosocial Intervention Delivery (RAPID) trial builds on the feasibility and acceptability data for a number of available digital interventions. Further details on trial procedures and methods can be found in the trial protocol, a brief overview is provided below.[1]

Aim of the trial

The trial aims to answer the question of which brief, remote psychosocial intervention for people with SMHPs who report recent suicidal ideation, or a suicide attempt is most clinically effective and cost-effective in comparison to TAU.

Objectives and/or research hypotheses of the trial

Compared to TAU, it is hypothesised that the remote interventions plus TAU will lead to:

1. A reduction in psychiatric hospital admissions over 6 months
2. A reduction in psychiatric hospital admissions over 3 months
3. A reduction in suicidal ideation over 3 and 6 months
4. An improvement in user-defined recovery and quality of life over 3 and 6 months

It was also hypothesised that interventions would be cost-effective over 6 months when compared to TAU alone, which is the focus of this health economics analysis plan.

The 6 month time frame accounts for expected inpatient admission rates in this population, as this outcome is both costly and should impact health benefits, 6 months was judged to be an appropriate time horizon for the economic evaluation. However, it should be noted the full impact on economic outcomes will occur over a longer time horizon.

Trial population

The trial is recruiting people with severe mental health problems (SMHP) who have had recent suicidal crisis and is being conducted in UK NHS crises services across five locations in England (East London, Greater Manchester, Northeast London and Oxford) and Scotland (Glasgow). The inclusion and exclusion criteria are reported in Table 1.

Table 1 Trial inclusion and exclusion criteria

Inclusion	Exclusion
• Currently receiving care from a Home-Based Treatment Team/crisis team or have done so within the last 14 days, since referrals to HBTT/crisis team are associated with increased risk of a psychiatric hospital admission in the near future • Aged 16+ • Meet criteria for a diagnosis of SMHP (schizophrenia spectrum, bipolar, major depressive disorder, emotionally unstable personality disorder (EUPD), PTSD or cPTSD) since these diagnoses account for the majority of PHAs for mental health difficulties • Experienced suicidal ideation or attempt within the last month/current crisis episode, as operationalised by answering 'yes' to items 1 or 2 of the Columbia-Suicide Severity Rating Scale • Able to provide informed consent • Receiving care from a Community Mental Health Team or Early Intervention Service, to ensure ongoing specialist mental health support following discharge from HBTT	• Organic impairment, as this could be the cause of mental health symptoms rather than a SMHP. • Non-English speaking, since two of the interventions are remotely delivered talking therapies and one of the interventions is a smartphone app which has only been developed in English. Provision for non-English speakers would be impossible on both financial and logistical grounds. • Primary diagnosis of a drug or alcohol dependence, as this could be the cause of mental health symptoms rather than a SMHP. • Moderate to severe learning disability as confirmed by the participant's responsible clinician in their care team. • For both ethical and safety reasons, immediate risk to others as confirmed by the participant's responsible clinician in their care team. • Currently receiving psychiatric inpatient care (since people in recent contact with crisis teams may have already been admitted to hospital).

Reproduced from Pyle et al. 2024 [1]

Intervention and comparator

Brief, remote interventions

SAFETEL: a brief, psychosocial intervention delivered by Assistant Psychologists (APs) employed by the NHS and delivered by telephone or videoconference in up to 12 sessions over a 3-month period.[21,22]

PREVAIL: a brief, psychosocial intervention delivered by Peer Support Workers (PSWs) employed by the NHS and is delivered by telephone or video conference in up to 12 sessions over a 3-month period.[23]

BrighterSide smartphone app: a self-guided smartphone app with five modules (available on installation and with flexible orientation) to help those with suicidal thinking to understand their thoughts and develop the best skills and strategies to help manage them.[24]

Note: BrighterSide (n=54) was dropped in April 2023. As the number of participants in this group is so low, this intervention will not be explored in the economic evaluation and these participants will be dropped from the health economics database. In September 2024, following an interim analysis PREVAIL was dropped from the trial, however this will be retained in the economic evaluation as the number of participants is sufficient for evaluation and the interim analysis was based on assessment of the primary outcome alone.

Treatment as usual (TAU)

Comparator: TAU consists of care delivered by multi-disciplinary crisis teams. As the trial includes multiple diagnostic groups who have different psychosocial interventions recommended in National Institute for Health and Care Excellence (NICE) guidelines, there is no suitable single active comparator.

Trial design

Originally the RAPID study design was a four-arm, multi-centre, superiority, randomised controlled trial (RCT) with an adaptive design with three remote interventions (PREVAIL, SAFETEL and BrighterSide). However, in April 2023 the BrighterSide arm (n=54) was removed (four-arm to three-arm) as a result of new evidence which demonstrated that the BrighterSide app did not have any significant improvement in suicidal ideation symptoms in the general population.[24] Previously, the randomisation ratio was 1:1:1:2 in favour of TAU, however this was amended to 2:2:3 in favour of TAU after the removal of the BrighterSide arm. Randomisation is via an independent remote web-based randomisation system using randomly permuted blocks, stratified by site. The expected sample size, inclusive of the three remaining arms, is 1064 participants (1118 inclusive of BrighterSide participants).

The primary outcome of the trial is psychiatric hospital admission at 6-month follow-up. Secondary outcomes include suicidal thoughts and behaviours, personal recovery, anxiety, depression, hope, entrapment and adverse effects. Further secondary measures were collected for the economic evaluation (EQ-5D-5L and Recovering Quality of Life (ReQoL-10), and service use.

Trial start and end date

The trial start date refers to the date on which first patient consented to participate within the trial, and the end date refers to the date on which the last patient follow-up was completed for the final participant. Details of these are provided below:

- Start date: 11th August 2022
- End date: to be confirmed

Health Economic Analysis Plan

Purpose of the HEAP

This document outlines the methods for economic evaluation conducted as part of the RAPID trial, including how data will be collected, analysed, and reported. The HEAP has been written following a review of the trial protocol and Statistical Analysis Plan (SAP) to ensure that there is consistency where possible. Note the contents of the HEAP follows the recommendations made by Thorn et al. 2021 [25].

Aim of the economic evaluation

The within trial economic analysis aims to estimate the cost-effectiveness of the included interventions (PREVAIL and SAFETEL) plus treatment as usual (TAU) versus TAU for people with severe mental health problems (SMHP) who have had recent suicidal crisis, from the perspective of the NHS and social care in a UK setting.

Note, although the PREVAIL intervention was dropped from the trial after an interim analysis (September 2024) data from this arm will be retained for the economic evaluation as it is sufficient for an analysis.

Objectives of the economic evaluation

The primary objectives for the trial cost-effectiveness analysis are to:

- Estimate the costs of health and social care service use in the interventions and usual care groups, and assess whether there are differences between groups
- Estimate the quality adjusted-life years (QALYs) of patients in the interventions and usual care groups, and assess whether there are differences between groups
- Assess whether any additional benefit is worth any additional cost

Overview of the economic analysis

The within trial economic analysis will be performed using patient-level data collected from the trial during baseline and follow-up (3-month and 6-month) study time points.

The economic analysis will use a within-trial, intention-to-treat (ITT) approach, and include all participants randomised to the three trial arms. The primary analysis will use the NHS and Social care (costs) perspective, as recommended by NICE, with a 6 month time horizon [26]. In addition, a service user perspective will be used for health benefits.

The primary analysis will take the form of a cost-utility analysis (a subset of cost-effectiveness analysis), with QALYs (EQ-5D-5L and published utility tariffs recommended by NICE at the time of the analysis) used as the measure of health benefit for the primary analysis. Multiple imputation will be used to impute missing observations. The analyses will control for key baseline covariates or characteristics (demographic, socio-economic and clinical measures) identified from the published literature and supplemented with analysis of pooled baseline data. Regression analysis, adjusted for key covariates, will estimate the net costs and QALYs of the intervention. The estimates of net costs and QALYs from the regression analyses will be bootstrapped to simulate a minimum of 1,000 pairs of incremental cost and QALY outcomes. Cost-effectiveness acceptability curves (CEACs) will be plotted to summarise uncertainty associated with the incremental cost-effectiveness ratio (ICER). To derive CEACs, the incremental cost and QALY (effect) estimates from the regression analyses will be bootstrapped to simulate the sample data of costs and QALY. The bootstrapped estimates of net QALYs will be revalued, using a range of ceiling ratios or willingness to pay thresholds (WTPT) to gain 1 QALY.

Sensitivity analyses will explore the intervention's cost-effectiveness by changing key methods and assumptions.

Jurisdiction

The trial will be conducted in England and Scotland, which has a national health service (NHS) and social care, providing publicly funded healthcare, primarily free of charge at the point of use.

Perspective

The primary cost-effectiveness analysis will take an NHS and social care perspective, in line with the NICE reference case (NHS and personal social services) [27].

A societal perspective will not be taken due to high unemployment in the population of interest, data collection burden and the trial time horizon. Unemployment in the population with SMHPs is high (recent work at King's College London estimated it to be around 80%) and subsequently a societal perspective is less relevant, especially in a sample of the population with suicidal ideation for whom employment has additional challenges.[28] Carer time would be interesting to consider as carers of people with SMHP face reduced employment rates. However, this was not collected within the trial and due to the short time frame employment changes are likely to take longer to materialise.

Time horizon

The primary economic analysis will compare the costs and health benefits (consequences) of each arm over the follow-up period of 6-months.

Statistical software

Descriptive analysis, data manipulation and the main economic analyses will be conducted using Stata V.14. or higher.

Identification of resources

The following items of healthcare resource use that may differ between study arms will be collected in the trial, this includes primary, secondary, and community-based health and social care services. Inpatient care is a key cost driver in this population, and as the primary trial outcome is reduced inpatient admissions, it is anticipated that if effective, this outcome will be reflected in costs.[29]

Measurement of resource use data

Resource/service use data will be collected from participants via the Economic Patient Questionnaire (EPQ), completed by research staff with participants at baseline, 3- and 6-month follow-up. The EPQ was developed from existing mental health EPQs held by the co-applicants and revised with the research team.[30–32] The EPQ will obtain data on any services used (i.e. inpatient, outpatient, accident and emergency, primary, community and social care use). Data on all services accessed is collected, i.e. physical and mental health-related service use. This is due to a significant interaction between mental health and physical health and challenges separating the two. E.g. in this population participants may require physical health visits related to suicide attempts. A separate form collects data on psychiatric hospital admission which is obtained by screening the participants' electronic patient records. This provides an alternative to the self-report data collected in the EPQ. An overview is provided in Table 2.

Table 2 Service use collection

Service type	Unit measure	Source
Hospital inpatient - psychiatric	Days per stay[a]	• Psychiatric hospital record • Economic Patient Questionnaire
Hospital inpatient - other	Days per stay	Economic Patient Questionnaire
Hospital day	Number of visits	Economic Patient Questionnaire
Hospital outpatient	Number of visits	Economic Patient Questionnaire
Accident and emergency	Number of visits	Economic Patient Questionnaire
Primary care[a]	Number of visits	Economic Patient Questionnaire
Community care[b]	Number of visits	Economic Patient Questionnaire
Notes: [a] will be used to guide the selection of appropriate unit costs by determining short or long stay, [b] examples include general practitioner; [c] examples include community-based mental health care and social support.		

Note that TAU will be collected within the EPQ, however as TAU is heterogeneous across settings and due to differences in the completeness of data provided by participants, this may be challenging to summarise. Sites will be asked to confirm what they believe TAU is, to help identify it within the EPQ data. For the economic evaluation, TAU will not be reported separately but will be costed within each of the categories above.

As there are two sources of data for psychiatric hospital admission, these will be costed and compared. It is assumed that the psychiatric hospital record will be the most reliable and subsequently, this source of data will be prioritised for the primary analysis, with the other services taken from the EPQ. Whilst the hospital record data are noted to be potentially more reliable (e.g. as they avoid recall bias) it was not possible to collect all health and social care service use due to challenges with data linkage and accessing patient records. The UK literature recognises that issues with electronic routine data sources may result in self-reported data being the preferred option.[33]

Valuation of resource use data

For the reported health and social care use, unit costs for services will be derived from national average unit cost data [34,35]. The price year for costs will reflect the most recent unit costs available at the time of analysis (currently 2023/24). The total direct health and social care costs of service use for each trial arm will be estimated by summing the costs of each resource by the reported use to provide health and social care.

Intervention costing

Intervention costs will account for staff time, including administrative time as well as delivery of sessions. Delivery is via videoconferencing or phone calls, which are covered by existing NHS budgets for these services and subsequently will be excluded from the intervention costing as they are incurred regardless.

Identification of outcome(s)

Health benefit for the primary economic analysis will be Quality-Adjusted Life Years (QALYs) derived from utility scores, obtained using the EQ-5D-5L quality of life instrument and published utility tariffs, as recommended by NICE at the time of the analysis. QALYs and the EQ-5D are used here, as this is the preferred measure of health-related quality of life in adults, according to the NICE reference case.[36]

While the EQ-5D is a commonly used generic measure of health, recommended for use, evidence on its responsiveness to change in mental health is contradictory.[37] The Recovering Quality of Life (ReQoL-10) is a self-report measure, which focuses on aspects of recovery and quality of life and was designed for use in a broad range of mental health conditions.[38] It was collaboratively developed with service users and clinicians. Furthermore, using a selection of the ReQoL, the ReQoL-Utility Index (UI), can be used to generate alternative utility scores.[38] The impact of this alternative utility score will be investigated in a sensitivity analysis.

Measurement of outcome(s)

Participants measurements (including the ED-5D-5L and ReQoL-10) will be collected at baseline, 3-, 6- months post allocation. Researchers collect measures by interview to assist with understanding and to minimise missing data.

Valuation of outcome(s)

Utility scores will be derived from responses to the EQ-5D-5L. UK utility values will be derived using the approach recommended by NICE, which is currently using the validated mapping function from the existing EQ-5D-3L. In line with current NICE recommendations, the mapping function developed by the Decision Support Unit (DSU) using the 'EEPRU dataset' will be used for reference case analyses [36]. The ReQoL-UI uses six-items (items: 3, 5, 6, 7, 9, 10) and one physical health item of the ReQoL-10.[38]

Total QALYs will be estimated as follows:

$$QALY = \Sigma[(U_i + U_{i+1}) /2] \times (t_{i+1} – t_i)$$

Here, U = utility value and t = time between assessments. The time between assessments is the time from baseline data collection to follow-up.

Mortality will be accounted for in QALY estimates as this is being collected by the trial team.

Analysis population

Analysis will follow intention-to-treat (ITT) principles, with the full analysis set to include all randomised participants.

If the proportion of adherence for any of the interventions is found to be lower than 80%, a sensitivity analysis will be conducted which includes only the participants who adhered to the interventions. For SAFETEL, adherence means attending the initial safety planning session and at least one follow-up call; for PREVAIL, this is defined as attending at least two peer support sessions.

Timing of analyses

The analysis will be conducted once all participants have completed 6-month follow-up and data has been entered. The within-trial primary analysis will take a 6-month time horizon and only use data obtained directly for participants. It should be noted that there are limitations to this time horizon, as it is unlikely to capture all of the costs and health effects between the alternative arms.[39]

Discount rate for costs and benefits

As the analysis will be conducted using a 6-month time horizon, discounting will not be required for either costs or benefits.

Cost-effectiveness threshold(s)

The willingness-to-pay (WTP) threshold in the UK commonly reported by NICE is currently between £20,000 and £30,000 per QALY [36]. However, while a previous review of NICE decisions suggested a WTP range of between £0 and £30,000 per QALY, more recent evidence has suggested that WTP thresholds closer to between £6,000 and £15,000 per QALY may be more appropriate [40–42]. Based on this evidence, the estimated mean QALYs and costs associated with each treatment option (PREVAIL plus TAU; SAFETEL plus TAU; TAU alone) will be compared against a range of values (£0 per QALY, £10,000 per QALY, £20,000 per QALY) for decision makers willingness-to-pay.

Statistical decision rule(s)

Mean differences in costs, QALYs and net benefits between the groups (PREVAIL plus TAU; SAFETEL plus TAU; TAU alone) will be estimated with associated 95% confidence intervals.

Analysis of resource use

Differences in the use of services used between randomised groups will be described but not compared statistically. Use of categories between groups will be compared individually (e.g. primary care, secondary care, etc.) and as total costs (at each assessment point). This will enable us to identify whether there are any notable differences in particular areas of service use between the groups.

Analysis of costs

Differences in overall mean costs between the arms will be analysed using a generalised linear model with gamma family, log distribution (to account for the skewed distribution of cost data). Minimisation variables of the randomisation process and key covariates will be included in the regression model to control for baseline factors that may influence costs. Covariates will be identified from recent published economic evaluations in this area, as well as guided by clinical and economic input.

In the event of participants with atypically high service costs, we may choose to exclude cost outliers from the primary analysis. Accurately estimating healthcare costs can be challenging as they can be skewed, whereby small numbers of patients use disproportionately more services than others.[41] Identified participants with ‘extreme’ values (i.e. values above the 95th/99th centile) will be discussed with the wider team to determine whether exclusion is valid. The exclusion rule will be applied to both arms of the trial, though it should be noted that given the likely high costs in this population and sample minimise the likelihood of this being necessity.

Analysis of outcomes

An appropriate regression model will be used to adjust for any imbalance in baseline utility and the minimisation variables of the randomisation process. Minimisation variables of the randomisation process and key covariates will be included in the regression model to control for baseline factors that may influence QALYs.

Data cleaning for analysis

Plausibility checks will be conducted on relevant data fields to check for any values which may be considered implausible (i.e. triple digit inpatient admissions since the SUI). Where problems are identified and timeframe permitting, data will be cross checked with original copies of recorded data from the original questionnaires. Additionally, manual checks will be conducted of the reported services used to identify any reported services which do not align to the stated perspective of the analysis. Where such services are identified, this data will likely be excluded however, instances of this will be reported. Checks will be conducted on the data (e.g. to identify minor errors in data entry) and any corrections will be accounted for in the Stata code. To aid analysis, 'other' service use descriptions will be cleaned and recoded. Where participants entered descriptions as free text, categories will be collapsed by the research team to simplify analysis (e.g. "bloodwork" and "blood tests" will be collapsed into a single description). This will allow key types of 'other' service use to be categorised and appropriate unit costs identified.

Missing data

Data will likely be missing, either from loss to follow-up or incomplete data collection, and the level of missing data for economic outcomes will be reported (costs and QALYs). Missing data will be accounted for in the analyses of net costs, net QALYs and cost-effectiveness acceptability. The methods used to deal with missing follow-up data will be determined according to the extent and pattern of missing data (e.g. multiple imputation, missing indicator or propensity score methods) [43–45]. Models used to impute missing data will likely be based on key covariates associated with costs or health benefits. Whilst very unlikely, if the level of missing data is very low (<5%) then data will not be imputed, aligned to good research practices guidelines.[46]

Analysis of cost-effectiveness

Cost and QALY data will be synthesised within an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) statistic from the NHS and PSS perspective.

The ICER is calculated as:

$$\text{ICER} = \frac{\text{Cost}_{\text{intervention plus TAU}} - \text{Cost}_{\text{TAU}}}{\text{QALYs}_{\text{intervention plus TAU}} - \text{QALYs}_{\text{TAU}}}$$

The ICER represents the additional cost of an intervention per additional QALY gained. Note that if the intervention is cost saving and produces more QALYs when compared to TAU, an ICER will not be presented as an intervention is dominant in such a scenario. Likewise, if the intervention is dominated it will be described in this way rather than calculated and presented numerically.

The NMB is calculated as:

$$\text{NMB} = (\text{incremental QALYs} * \text{WTPT}) - \text{incremental cost}$$

In addition to the above (in which each intervention is compared with TAU), a fully incremental analysis will be used which ranks the arms sequentially in order of effectiveness (or costs). This analysis accounts for the interventions being mutually exclusive. Different decision-makers may have reasons for favouring one intervention over another intervention (e.g. only one intervention may be feasible in their setting due to staffing requirements), and

subsequently presenting both a fully incremental analysis, plus ICERs for each intervention plus TAU, versus TAU, hopefully ensures that audiences have the cost-effectiveness findings they need.

Sampling uncertainty

Nonparametric bootstrapping will be used to investigate sampling uncertainty. Net cost and QALY estimates from the regression analyses will be bootstrapped to simulate a minimum of a minimum of 1,000 pairs of costs and QALY outcomes. The distribution of the bootstrap iterations will be plotted on a cost-effectiveness plane to assess parameter uncertainty (the spread and location of the data points will provide a visualisation of uncertainty). The bootstrap resampling estimates will also be used to construct a cost-effectiveness acceptability curve (CEAC), which will provide a visual representation of the probability of the interventions being cost-effective at different willingness-to-pay threshold values.

Subgroup analysis/analysis of heterogeneity

Patient heterogeneity is defined as natural variation across people, which can be explained by their characteristics (e.g. age, employment, symptoms).[47] The RAPID trial collects data on: age, gender identity, ethnicity, education, employment, marital status and living arrangements, diagnosis, symptoms, recent admission to an inpatient unit, and religious beliefs. There are no pre-specified subgroup analyses within the SAP. However, homogeneity in treatment effect (the focus of clinical studies) does not imply homogeneity of cost-effectiveness (as discussed by Grutters et al, 2013).[47] Cost-effectiveness studies need to consider wider sources of heterogeneity, e.g. related to baseline event rates.[48]

It should be noted that any investigation of patient heterogeneity will be limited by sample size and is purely explorative. It is not intended to guide decision-making at this stage but rather to highlight uncertainties between subgroups of the population that may necessitate further research and exploration.

The RAPID trial is a unique opportunity to investigate patient heterogeneity in a within-trial cost-effectiveness analysis in a population with SMHPs due to the sample size. A recent review of methods to account for patient heterogeneity found that recent publications focused on machine learning techniques.[49] Bonander and Svensson reported causal forests as a data-driven way to identify causal effect functions and heterogeneity in cost-effectiveness outcomes (incremental health benefit, incremental cost and net monetary benefit [NMB] due to patient characteristics/subgroups.[50] This technique has been used in recent cost-effectiveness studies but not within populations with SMHPs. This is a data-driven approach to learning patterns of heterogeneity that does not require researcher assumptions as fully as comparative techniques. For example, cut-offs do not need to be specified for continuous variables. However, the authors do note that causal forests perform poorly with smaller samples and suggest a minimum of 250-500 participants within a dataset. As cost data in populations with SMHPs is often skewed it is anticipated that a higher sample size would be needed and subsequently, a causal forest approach will be taken to investigate patient heterogeneity if complete economic data are available for a minimum of 500 participants with a sufficient sample in each arm.

In the event that the data are not judged to be sufficient for a causal forest approach, a more exploratory incremental net-benefit regression (INBRA) will be used. INBRA is a regression analysis in which the treatment dummies, relevant population characteristics (e.g. gender and ethnicity) and their interaction are regressed on net-benefits. This approach has been previously utilised in mental health cost-effectiveness research.[51] This more simple approach does require more definition and assumptions regarding potential subgroups when

compared with the causal forest approach. However, it will still aid in informing future economic evaluations.

Key subgroups were discussed with the PPI groups, as well as the trial team. Key patient characteristics for consideration by the PPI group were taken from the findings of a consensus exercise which aimed to identify patient characteristics that should be considered for inclusion in economic evaluations in SMHPs.[52] Potential subgroup analyses are included with rationale in Table 3. It should be noted that for the purposes of this exploratory approach, subgroups will not be restricted to those defined within the HEAP.

Table 3 Key subgroups

Subgroup	Rationale
Employment status	The RAPID PPI feedback noted that investigating cost-effectiveness by employment status would be interesting. Evidence demonstrates that being employed is positively associated with treatment recovery in people with SMI.[53] Furthermore, employment is also likely to be related to health and social care use and health status more generally. The demographics form captures at baseline whether the participant is in paid employment (full or part-time), undertaking other productive activities (e.g. voluntary work or education) or retired or unemployed. Note this is not collected at follow-up, so employment cannot be used as an outcome (further, we would not expect it to change within the time horizon). It is anticipated that the proportion of unemployment will be high (a recent study found that ~77% of people with SMI were economically inactive).[54] Subsequently, this subgroup analysis will explore cost-effectiveness in the group of RAPID participants who are economically active at baseline.
Prior admission to an inpatient unit (6 months prior to baseline)	The RAPID PPI feedback discussed that recent prior inpatient admission would be a useful indicator of how well someone is at entry to the trial. From the service use, we will know if a participant had an inpatient admission (related to mental health) 6 months prior to baseline. Furthermore, this is likely to be an indicator for service use/costs and health status. Therefore, this subgroup analysis will explore cost-effectiveness in the group of RAPID participants with an inpatient admission (related to their mental health) at baseline.
Diagnosis	The RAPID study includes participants with diagnoses of SMHPs, such as psychosis, bipolar and emotionally unstable personality disorder (EUPD). Diagnosis is likely to relate to health and social care use, as recommended care and clinical pathways differ by diagnosis, as well as health status. This subgroup analysis will look at key diagnostic groups (to be decided after reviewing the size of groups at baseline) and will explore how cost-effectiveness outcomes differ by group.
Religion and/or ethnicity	The RAPID PPI groups noted that characteristics that act as a proxy for cultural differences between participants (e.g. religion and ethnicity) would be useful to explore as this affects

	willingness to access services/seek help as culturally there may be higher stigma faced by some groups.
Abbreviations: EUPD, emotionally unstable personality disorder; SMHP, severe mental health problems.	

Before undertaking INBRA, we will explore whether the subgroups are different from the full sample and from each other in terms of: baseline utility, baseline costs, and likelihood of complete economic data (EQ-5D and service use) across all time points and likelihood of adherence to intervention. We will also look at the number and proportion of the sample in each group. This will help to contextualise any significant findings. It is noted that multiplicity becomes an issue when multiple subgroups are compared, as differences between subgroups can occur by chance, subsequently, caution will be taken when interpreting the results. It should be noted that the RAPID PPI had no concerns with any of the collected characteristics being explored.

The PPI group also reflected on unmeasured patient characteristics which may be important in this population. It was speculated that the following may be important:

- Prior treatments (focusing on psychological therapies) may be important as a proxy for how receptive people are to accessing care
- Area deprivation (requires postcode) which was discussed as impacting access to services and community support
- Adverse childhood experiences which impacts trust in services
- Family and generational history which impacts understanding on mental health and accessing services/treatments
- Homelessness, alcohol/drug use and contact with the criminal justice system were discussed as affecting the ability to engage with services/treatment, as well as mental health

Stigma (related to the characteristics above) was noted to play a part in service use (mental health and more generally). Whilst these characteristics cannot be investigated, the limitations of not having these data will be discussed in outputs and the list will be retained for future research.

Sensitivity analysis

Sensitivity analyses will be conducted if data are sufficient to explore uncertainties surrounding key parameters in the economic evaluation (Table 4).

Table 4 Planned sensitivity analysis

Analysis	Changes	Rationale
Complete case analysis	Removal of participants with incomplete/missing data	Using only the observed data will provide insight to the result for the group of participants with complete follow up and complete data (evaluable cohort). The results of the complete case analysis will be compared to the primary analysis (using multiple imputation) to give an indication of how robust the cost-effectiveness estimate is to the assumptions around missing data.
Adherence	Removal of participants who did	Using only the participants who adhered to the interventions, this analysis will explore

	not adhere to intervention	whether intervention is more or less cost-effective in participants who comply. Note aligned to the SAP this will only be conducted if the proportion of adherence for any of the interventions is found to be lower than 80%,
Alternative utilities	Use of ReQoL-UI generated utilities scores (rather than EQ-5D-5L)	As noted the ReQoL-10 is a measure more focused on aspects of recovery and quality of life in mental health conditions.[35] Using a selection of the ReQoL, the ReQoL-Utility Index (UI), can be used to generate alternative utility scores.[35] These utilities will be used to estimate alternative QALYs in a sensitivity analysis. It should be noted that the RAPID PPI team had a strong preference for the ReQoL-10 reflecting more aspects of health that were important to them, as well as being clearer and easier to understand/complete. However, to date there are no published studies looking at the validity of the ReQoL-UI in populations with SMHPs and subsequently, the EQ-5D will be the primary source of utilities as there is some evidence to support the use of the EQ-5D in this population, albeit mixed.[37]
Intervention costing	Inclusion of training costs	Training costs, which are sunk costs, will not be included in the primary analysis as NHS workers are continually developing and training is quite standard. Furthermore, assumptions around training (e.g. how long learnt techniques are applied, caseloads, etc) make it challenging. For a sensitivity analysis training will be included in the cost of intervention delivery.
Measure of benefit	Suicidal thoughts and behaviours (as measured by the Columbia-Suicide Severity Rating Scale [CSSRS])	Secondary analyses will explore the cost-effectiveness of interventions using a problem-specific measure of effectiveness, rather than the generic QALY. The PPI groups reviewed the secondary outcome measures and decided that suicidal thoughts and behaviours (as measured by the Columbia-Suicide Severity Rating Scale (CSSRS) would capture key aspects of health for the trial population group but would not be reflected in the EQ-5D or ReQoL measures. This will look at the cost per point change in the CSSRS, unless a clinically meaningful change is available. Note, this analysis will only be done if there is a clinically significant change in this

		measure as determined by the clinical effectiveness evaluation outlined in the SAP.
	Personal recovery (as measured by the Process of Recovery Questionnaire [PRQ])	The PPI team discussed personal recovery would be in part be covered by the ReQoL-10 measure, however felt it would still add to the analysis. This will look at the cost per point change in the PRQ, unless a clinically meaningful change is available. Note, this analysis will only be done if there is a clinically significant change in this measure as determined by the clinical effectiveness evaluation outlined in the SAP.
	Hope (as measured by Adult HOPE Scale [AHS])	The PPI team hope may be useful for the analysis, though again this may overlap somewhat with the ReQoL-10 measure. This will look at the cost per point change in the AHS, unless a clinically meaningful change is available. It was noted by clinical members of the team that this measure is very simplistic and subsequently it may be limited in terms of usefulness. Note, this analysis will only be done if there is a clinically significant change in this measure as determined by the clinical effectiveness evaluation outlined in the SAP.
Notes: Adult HOPE Scale, AHS; Columbia-Suicide Severity Rating Scale, CSSRS; Patient and Public Involvement, PPI; Process of Recovery Questionnaire, PRQ; Recovering Quality of Life – Utility Index, ReQoL-UI.		

Decision analytic modelling

Decision analytic modelling is not within the scope of this evaluation. However, if there is a difference in effectiveness between the interventions and TAU, and evidence to suggest that intervention offers benefits over a duration longer than the trial follow-up (i.e. > 6 months) the value of modelling will be discussed.

Approach to engagement with patients and others affected by the study

Note this section has been added to align with the CHEERS reporting standards, which highlight a greater emphasis on stakeholder engagement within cost-effectiveness studies.[55]

As detailed above, the RAPID PPI groups were consulted to support three key areas:

- Strengths and weaknesses of the EQ-5D and ReQoL-10 measures
- Secondary outcomes to be used in sensitivity analysis using alternative measures of health benefit
- Key aspects of patient heterogeneity (measured and unmeasured), with a focus on viable subgroup analyses

Planned dissemination

Findings will be published within the final NIHR report and the within-trial cost-effectiveness analysis will be published as a standalone journal publication. Furthermore, it may be presented at relevant academic conferences.

Reporting standards

The updated CHEERS 2022 28-item checklist will be followed when reporting the components of the health economic evaluation.[55] The completed CHEERS checklist will be made available within the supplementary materials.

Reporting deviations from the HEAP

Any deviation from HEAP will be described and justified in the final outputs (e.g. peer reviewed publications).

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