Relatives Education and Coping Toolkit (REACT) Study

Health Economics Analysis Plan

V1.4

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1 Introduction

This document details the planned health economic analysis for a randomised controlled trial to evaluate the clinical and cost-effectiveness of a peer supported self-management intervention for relatives of people with psychosis or bipolar disorder. Full details of the background to the trial and its design are presented in the trial protocol. The goal of the current research is to estimate the cost-effectiveness of the full REACT toolkit plus an online comprehensive resource directory and treatment as usual (REACT + RD + TAU) compared to an online comprehensive directory and treatment as usual (RD + TAU).

1.1. Study background

Relatives of people with psychosis/bipolar disorder (BD) provide a large amount of unpaid care with a very significant personal cost in terms of levels of distress and burden and, as a consequence, an increased use of health care services.
Online interventions are now well established in the treatment of many mental health conditions including depression and anxiety. Online support is also being developed to support relatives of people suffering from other chronic health conditions. This type of support may be particularly useful for this group of relatives due to the flexibility of use and the empathy and support that can come from being linked to other carers in similar situations.

REACT is a primarily online two arm pragmatic single blind individually randomised controlled trial lasting 24 weeks aimed at relatives, defined as family, partners or close friends, of people with psychosis or BD living in the UK (confirmed via valid postal address). Participants in both arms of the trial can access the intervention site whenever they wish throughout the period of the trial (minimum of 24 weeks to last follow-up for final participant). Participants are not required to adhere to a prescribed level of resource use; instead they are advised to use the intervention (REACT or RD) according to their level of need. All participants continue to receive whatever other current treatment or support they are offered.

The primary outcome is relatives' distress at 24 weeks assessed using the General Health Questionnaire (GHQ-28) using the Likert scoring (1-4). Secondary outcomes include the relatives' experience of caring assessed using the Carers' Well-Being and Support Measure (CWS) [33] [41], assessed at 24 weeks, and both distress (GHQ) and carer experience (CWS) assessed at 12 weeks follow-up.

1.2. Health Economics Objective

The REACT trial objectives, inclusion criteria, sample size, endpoints and analysis plan are described within the study protocol.

This document describes the planned cost-effectiveness analysis where the objective is to establish the relative cost-effectiveness of REACT toolkit and RD using incremental cost and cost-effectiveness analyses using a standard instrument to assess health related quality of life – the EQ-5D-5L.

1.3. Health Economics Analysis Plan

The objective of this analysis plan is to describe the cost-effectiveness analyses to be carried out for the REACT randomised controlled trial for the final analyses. It does not address the trial analysis set out in the Statistical Analysis Plan (SAP). Analysis will be conducted in Excel, producing estimates of cost-effectiveness to generate (within trial) incremental cost-effectiveness ratio (ICER) planes and cost-effectiveness acceptability curves (CEAC) using standard methods.

2 Analysis

2.1. Study perspective

All analyses will be at the participant level and a NHS perspective will be taken.

2.2. Time horizon

As this is a within trial analysis, both changes in the EQ-5D-5L and costs will be done for 6 months.

2.3. Outcomes

2.2.1 Resources

An adapted version of the Client Service Receipt Inventory (CSRI) will be used to collect online retrospective information about the participant's use of health and social care services, accommodation and living situations, income, employment and benefits. Days lost by relatives

from work, and reduced hours while at work due to the caring role will also be recorded and costed as part of the CSRI. Resource assessment occurs at baseline, 12 and 24 weeks.
We will include use of other free interventions including relatives support groups and websites, so we can accurately describe current treatment. Unpaid informal care by the relatives will be measured by asking relatives how many hours of care they provide supporting the person with mental health problems,
Healthcare resource use will be costed using published national reference costs. The British National Formulary Tariffs will be used to cost medications. To value healthcare resources the PSSRU Costs of Health and Social Care will be used. Time off work will be costed on an hourly basis based on national mean age and gender specific wage rates available from the Office for National Statistics. The cost of the intervention based on trial costs will be considered in the primary analysis, taking into account the 400 participants receiving the intervention and the 801 recruited. Implementation costs will be derived from IMPART and included in the sensitivity analysis
Participant level costs will be estimated as the sum of resources used weighted by their national reference costs and the costs of the intervention. Effect of treatment on resource use and cost will be estimated using Student's t-test for unpaired data.

2.3.2 Quality of life

The trial includes the use of the EQ-5D-5L questionnaire, which will be completed at baseline, 12 and 24 week. Repeated scores over time will be used to obtain estimates for each patient. The within trial difference between baseline and week 24 expressed as quality-adjusted life years (QALYs) will be estimated using the EQ-5D-5L result with the EQ-VAS providing supportive estimate. A linear change approach will be used adjusting for baseline imbalance in mean utility. No discounting will be applied taken into consideration the follow-up period below 1 year. Effect of treatment on health related quality of life will be estimated using Student's t-test for unpaired data.

2.3.3 Calculation of parameter values

- The five components of the EQ-5D-5L can be assigned level 1, 2, 3, 4 or 5. The resultant health states described by the EQ-5D-5L will be scored using the UK value set estimate by Devlin et al. (2016). If at least one of the components is missing the EQ-5D-5L will also be set to missing.
- Adjustments for baseline imbalance in mean utility will performed.

- Descriptive statistics will be reported for change in EQ-5D-5L scores during the intervention between the two arms of the trial and 95% confidence intervals
- Unit costs of the resource use items recorded in the CSRI will be derived from sources relevant to the UK NHS.
- Costs will be expressed in current year (2018) GBP. The Health Service Cost Index will be used to adjust costs to the current price year where necessary.
- Descriptive statistics will be reported for each resource use item.

2.3.4 Cost-effectiveness analysis

Overall mean costs, stratified by NHS & PSS, and standard deviations for both arms of the trial will be calculated. Patient level total costs and quality of life data will be bootstrapped to generate incremental cost-effectiveness (ICER) planes, to estimate average (median) cost-effectiveness and 95% confidence intervals. Uncertainty around cost-effectiveness will be described using cost-effectiveness acceptability curves (CEAC), which are used to describe the probability of an intervention being cost-effective (Drummond et al., 2015).

2.3.5 Sensitivity Analysis

The use of a decision analytic model can introduce uncertainty around the assumptions used, such as the health states described and data sources selected. With sensitivity analysis in parameters such as resource use, costs, number of users and effectiveness, for example, aspects of model uncertainty be will be addressed. Further to this a complete case analysis and an analysis REACT vs. treatment as usual and with the addition of costs from the IMPART implementation plan will also be done. By using alternative assumptions the robustness of the ICER can be ascertained.

2.3.6 Missing data

- Patterns of missing data will be presented.
- Sensitivity to missing data will be assessed by comparing the characteristics of the patients with missing items to those with complete data.

- Multiple imputation of missing items will be undertaken and the estimation of parameter values will be based on the appropriate pooled statistic from analysis on each of the multiply imputed datasets.

2.4. Updating the economic analysis plan

Due to different reasons changes to existing analysis might be deemed as necessary

- Dated changes to the analysis plan will be documented in this section.
  Circumstances under which changes will be allowed are as follows.
    - Development of novel statistical methods that are deemed more appropriate for this analysis.
    - Clarification of currently debated issues.
    - Preliminary data cleaning or analysis (conducted prior to unblinding) suggesting that planned analyses are sub-optimal.