Research recommendations for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Research question

What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to an initial psychological intervention for the current episode?

Why this is important

Not all people with depression respond well to first-line treatments and approximately one-third do not fully recover with first line treatment and may remain symptomatic even after a second-line treatment. Finding improved models of treatment for people who do not respond to first-line treatment is critical. We do not know what treatment options best follow inadequate response to a first-line psychological intervention, including adding antidepressant medication or switching to another psychological intervention or how to make this choice.

Table 160: Research recommendation rationale

Research question	**What are the relative benefits and risks of further psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to an initial psychological intervention for the current episode?**
Why is this needed	
Importance to 'patients' or the population	Depression is a debilitating and highly prevalent condition in adults. Despite significant investment in 'Improving Access to Psychological Therapies' (IAPT) services, the most effective, evidence-based and well-established treatments have only modest effects on depressive symptoms. In addition, many people relapse from an episode of depression. More effective treatments for a single episode of depression are needed. The definition of 'Treatment-resistant' depression is disputed, but includes failure to respond to at least two antidepressants (ADs) from different classes and there is no consideration of response to psychological interventions.. Further research on the identification and management of treatment-resistant depression is required.

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Relevance to NICE guidance	The guidelines currently make recommendations for further-line interventions and for treatment-resistant depression but there is uncertainty as to what interventions are most effective in response to an initial psychological intervention, given that most evidence is based on initial treatment with antidepressant medication. improved evidence for effective further-line treatments following unsuccessful first line psychological treatment could lead to greater clarity in the recommendations.
Relevance to the NHS	Use of more effective and more cost-effective options may lead to reduced costs for treating people with acute depression. Evidence on the sequencing of psychological interventions may lead to improved IAPT service delivery.
National priorities	The NHS Five Year Forward plan and NHS Long Term plan make access to effective mental health services a key national priority.
Current evidence base	The current evidence base for further-line treatment is predominantly based on antidepressant medication as the first line of treatment. Treatment resistant depression (TRD) is usually defined as a failure to respond to 2 adequate courses of antidepressants within a specified episode of depression, without consideration of response to psychological interventions. With increasing access to psychological interventions (via IAPT) and many patients expressing preference for psychological interventions, increasing numbers of patients with depression may have a psychological intervention as the first-line treatment. However, there is uncertainty as to what to do next, whether to switch to antidepressants, switch to another psychological intervention, continue the psychological intervention and add antidepressant medication. Very little evidence is available which identifies what are the most effective and cost-effective interventions following an unsuccessful first-line psychological intervention.
Equality	NA - No equality concerns identified
Feasibility	This research would require a series of RCTs utilising different designs and comparisons (e.g., switching psychological interventions, switching to antidepressant medication, augmentation with

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	antidepressant medication) to identify which further-line interventions are most effective. These novel treatments should then be tested in large scale RCTs against current most effective psychological treatments. This would require an extensive programme of research. Numbers of people treated for depression in primary care make this study feasible.
Other comments	NA

NA: not applicable

Table 161: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults in a depressive episode whose depression has not responded or there has been limited response for the current episode or residual depressive symptoms following initial psychological treatment(s)
Intervention	Psychological interventions: • Behavioural therapies • Cognitive and cognitive behavioural therapies • Counselling • Interpersonal psychotherapy • Psychodynamic psychotherapies • Psychoeducational interventions • Self-help with or without support (facilitation) Antidepressant medications including SSRIs, SNRIs, TCAs Physical interventions including ECT and touch therapies
Comparator	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo
Outcomes	Critical: • Depression symptomatology • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Criterion	Explanation
	Important: • Quality of life • Personal, social, and occupational functioning
Study design	Randomised controlled trials
Timeframe	Minimum follow-up 6 months after end of treatment; additional follow-up at 2 years
Additional information	The randomised controlled trials can include a range of designs to test switching/augmentation such as adaptive and SMART designs. It would be helpful to collect data that supports the development of treatment decision rules.

ECT: electroconvulsive therapy