Title: Addressing the Challenges of Early-Phase Research (ACER): Design Considerations in trials of medicinal products for depression

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Background

Depression is a common mental health illness whereby patients experience sustained low mood which adversely affects quality of life, social and occupational functioning[1]. Depression can vary in severity from mild to severe, with the treatment of the illness depending on the severity. In some cases, no treatment is provided and for others it can be lifestyle changes, psychological therapy and/or drug treatment[1].

The NHS prescribed around 89 million antidepressant drug items in 2023/24[2]. From the NHS Business Services Authority Statement, from April to June 2024, 23 million antidepressant items had been prescribed to an estimated 6.9 million patients[3]. The cost of these items for the quarter is £55 million[3].

Some drugs prescribed for depression are believed to worsen the underlying condition[4,5] and can have further side effects, which lead to drug withdrawal within the UK and across the globe. Esketamine is used to treat depression however side effects include anxiety, suicidal ideation, fatigue, insomnia, depressed mood and pain[6]. Similar side effects occur for other drugs used to treat depression (Paroxetine, Sertraline, Fluoxetine and Fluvoxamine) but can also be experienced with the withdrawal of the treatment[7]. Therefore, it is key that the safety profile of a drug is understood prior to its release to the market.

The trial design used in early phase research has an impact on the understanding of the safety profile of the drug prior to its progress to a later phase trial and potential release to market. For the purpose of this research an early phase trial will be defined as either a phase I or phase II trial whereby they are the "first step in testing new medicines that have been developed"[8]. We will include rolling/seamless phase 2-3 trials in this definition with the focus in these cases on the design of the phase 2 aspect.

Historically, the 3+3 design has been commonly used for early phase dose finding trials, whereby patients are treated in cohorts of three and the decisions on the safety of the drug are made at the end of each cohort. Other designs can also include the use of single arms such as continual reassessment method (CRM) and accelerated titration design (ACT)[18]. However, Bayesian and adaptive designs have been developed for use in early phase research[9] which allow for additional information and analysis to be included in the design such as varying cohort sizes, prior knowledge of the drug, addition and/or removal of treatment arms. An example of an innovative design used for early phase research is a Bayesian design that allows prior knowledge of the drug to be used. The knowledge gained throughout the trial can then be used to update the decision-making model. Adaptive trial designs are defined by the FDA as "a clinical trial design that allows for prospectively planned modifications to one or more

aspects of the design based on accumulating data from subjects in the trial."[10] .Both Bayesian and adaptive designs for early phase research have grown within the cancer field, however this may not correlate across other areas.

Thes recent advancements in Bayes and adaptive designs for early phase trials could have benefits within the mental health setting. It is important to understand whether these methodological advancements are now being utilised.

We aim to assess the influence on the knowledge of a drug's safety profile by reviewing the trial designs employed and focusing on early phase and Bayesian/adaptive design use. Given the increasing use of Bayesian and adaptive designs in clinical trials, it is important to understand their role in shaping knowledge of drug safety. This could be key for drugs being withdrawn from the market as potential improvements to the trial design could provide better understanding of the drug safety profile thereby reducing drug withdrawals from the market.

The study objectives are:

1. To gain an understanding of the trial designs used in early phase depression clinical trials
2. Examine the advantages and challenges faced is using adaptive methods in early phase depression clinical trials
3. Implications of the trial design on safety

Methods

This study was a review of the literature, whereby data was extracted from early phase trials in depression to describe the designs used and trial features. The databases searched were clinicaltrials.gov[13], VIVLI[14], CSDR[15], Pubmed[16], and Cochrane[17].

The following phrases were used to search the databases: Depression, Depress, Mental Health, Low mood, Major depressive disorder, MDD and Antidepressant. We aimed to identify trials completed between 2000-2025. The following inclusion criteria were applied to the search results and used to identify eligible studies:

- Early phase trial – Phase I (a or b),II (a or b), I -II or II - III
- Condition studied – depression
- Intervention of interest is a medicinal product

Data collected on eligible trials included trial design, treatment studied, phase of the trial, adaptive and Bayesian features, sample size required and achieved, year of trial start, length of follow up for primary outcome and number of doses/treatments. These data have been categorised and reported by frequencies and percentages using the number of trials included as the denominator. Where appropriate graphical summaries are presented.

The methodology in each trial was reviewed and the impact of using a particular design compared to other Bayesian and/or adaptive designs discussed with a focus on the potential impact on drug safety knowledge.

The data collected on each drug studied are reviewed in line with the trial design information. Potential improvements to the trial design are investigated to see if this could improve knowledge of the drug safety profile.

Results

Figure 1 presents the search results from the databases with 216 trials eligible for inclusion. The most common reasons for ineligibility are trials that where not depression (this included trials of comorbidities) and trial treatment was not a drug, these largely included behavioural/psychological therapy or transcranial/electromagnetic stimulation.

Trial characteristics are given in Table 1. Of the 216 eligible trials, 190 (88%) included randomisation and only 35 (16%) included an adaptive/Bayesian element to the trial design. These elements included interim analysis allowing for adjustments, dose changes based on participant response and a review committee to make dosing decisions following a cohort completion. The most common interim analysis adjustments included changing the randomisation ratio (N=3), reducing sample size (N=4), change to dosing regimen (N=2), dropping arms (n=1) and terminating the study (N=4). Some trials did not stipulate the role of or that they had a review committee, therefore the level of independence, the constitution and remit was unclear of such a committee.

Information on the drugs used in trials included in the cohort are given in Table 2. There was a total of 117 different drugs studied in this cohort and 25 (21%) have been withdrawn from development largely by the company (N=23). 60 (51%) are still under investigation for depression, or were considered as a repurposing of the drug for depression. A placebo was used in 168 (78%) of the trials included. In these trials placebo was used as either an inactive standalone comparator or adjunct therapy for example Citalopram+Riluzole against Citalopram+Placebo.

The majority (N=25 (96%)) of the non-randomised trials where single arm and 8 (31%) included an adaptive or Bayesian feature which involved changes to dosing regimen, two stage/phase design and safety review committee for dosing decisions. The occurrence of adaptive and/or Bayesian features were more common in single arm non-randomised trials (32%) than in randomised trials (14%). The trials that included the drugs which were not withdrawn (N=101) are predominantly randomised trials 86 (85%) with 14 single arm studies, of which 9 and 5 respectively contained an adaptive or Bayesian element.

Discussion/Conclusions

There were a total of 35 trials of those studied between 2000 and 2025 (N=216) that included at least one adaptive and/or Bayesian feature, of which nine included an interim analysis while 21 included dose changes and/or safety review committee for dosing, 4 included a two stage/phase design and one SMART design. The use of adaptive and Bayesian designs/features in early phase trials for depression do not seem to be common. The most

common design is a parallel randomised controlled trial (N=167 (77%), of which 109 are two armed).

Our cohort included four trials containing five arms, one was phase I and three phase II. In each trial one drug was administered at a different dose for each arm, with no adaptive or Bayesian design features. The use of adaptive designs as an alternative would have greater efficiencies. The sample sizes of these studies appeared large for their phases (260, 108, 889 and 976). A clear purpose of an early phase trial is to understand drug safety while exposing a minimal number of patients to a drug. This is a key feature of an adaptive design[19].

In these cases, a dose escalation trial design could be utilised to understand and determine the safety and tolerability of the treatments, as well as signals for efficacy, prior to selecting the doses to further study. Another alternative would be an adaptive trial with an interim analysis with the ability to drop arms for safety or futility, a multi-arm multistage (MAMS) design could be used. Both suggestions have potential to reduce the trial sample sizes and reduce the potential risk to patients of receiving a drug that is not safe/tolerable or that is not efficacious[19].

Furthermore, of the excluded trials some of the comorbidities studied (e.g. sexual dysfunction) seem to be a comorbidity that could be a result of the treatment they are receiving for the condition of depression. This could be a topic for future discussion and research.

Many of the antidepressants not withdrawn from market come with a suicidality warning on thoughts and behaviours, especially for under 25s (for example Ketamine, Citalopram). The FDA mandated in 2004 for some of these drugs to contain a black box warning for these, however this has become a topic for discussion among researchers[12].

Following the black box warning for young adults (under 25s) various studies and reports have been produced on antidepressants usage, suicidality and other behaviours. Some studies suggest that there has been a reduction in antidepressants prescribed, with no increase in suicide rates but there has been an increase in psychotropic drug poisonings and overdoses[22,23]. The warning has also been linked to patient hesitation to take antidepressants once diagnosed.[12] These aspects would need to be considered within future trial designs. An adaptive design, potentially a platform trial, would be beneficial here, to investigate the suicide warning, rather than a standard randomised controlled trial, as interim analyses can be built into the trial to stop for futility or safety concerns. For example, multiple arms could be tested at once using a MAMs or other platform design with pre-planned interim analysis that allow for arms dropped due to safety as applicable.

Among the drugs not withdrawn side effects include: suicidality, dissociation, sexual dysfunction, sleep affected (including unable to sleep, insomnia, affect dreams), anxiety and mood swings/emotional distress. Side effects for the drugs not withdrawn and being investigated for the use in depressed patients include the signs and symptoms of the original

condition that is to be treated. A further topic on this could be the investigation of the true source of the side effects listed for the drugs, this being the treatment at hand or the signs and symptoms of the condition itself. Of the drugs withdrawn from development, only four had safety concerns as one of the reasons for withdrawal, 18 were due to lack of efficacy/effectiveness and five did not specify a reason.

Across all the trials in our dataset 27 (12%) trials were terminated prematurely, in 2013 a review of clinicaltrials.gov found that 12% of trials here terminated[20], while a more recent review across trials found termination rates to have decreased from 10.6% to 4.7% from 2010 to 2021[21]. In our cohort, nine (38%) of those terminated prematurely had an adaptive design with five ending due to interim analysis/safety and the other four due to funding, data from other studies, sponsor decision and study team decision. Other trials terminated were mainly for the following reasons: recruitment challenges, funding and sponsor decision. Overall, 25.7% (9/35) of the trials with adaptive/Bayesian features were terminated compared to 8.15% (15/184) of those that did not. A bayesian and/or adaptive trial design can allow the data to be monitored more closely and therefore, provide the study team with more information sooner on the trial treatment that could lead to termination.

A strength of this study is that trials from the last 24 years have been investigated (start years 2001-2024) with a range of responses across features including trial design, primary outcome follow up length and duration of the trial.

A weakness of the study is that we focused the research on drug treatment for depression. Adaptive and Bayesian trials designs/features can be incorporated into trials of other treatments for depression including transcranial/electromagnetic stimulation. This study also highlights that trial designs used in depression are behind those used in other disease areas such as cancer.

This study was a review of completed early phase trials in depression where the intervention is a medicinal product. From the study there appears to be little uptake in the use of adaptive and Bayesian features and/or design in trials of a drug for depression treatment. Approaches that may improve the use of adaptive and Bayesian designs, include promotion in mental health journals, as well as discussion and dissemination of information at conferences and within the community.

Future work - We are currently drafting a manuscript to submit to TRIALS.

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Appendix

Figure 1 Screen results

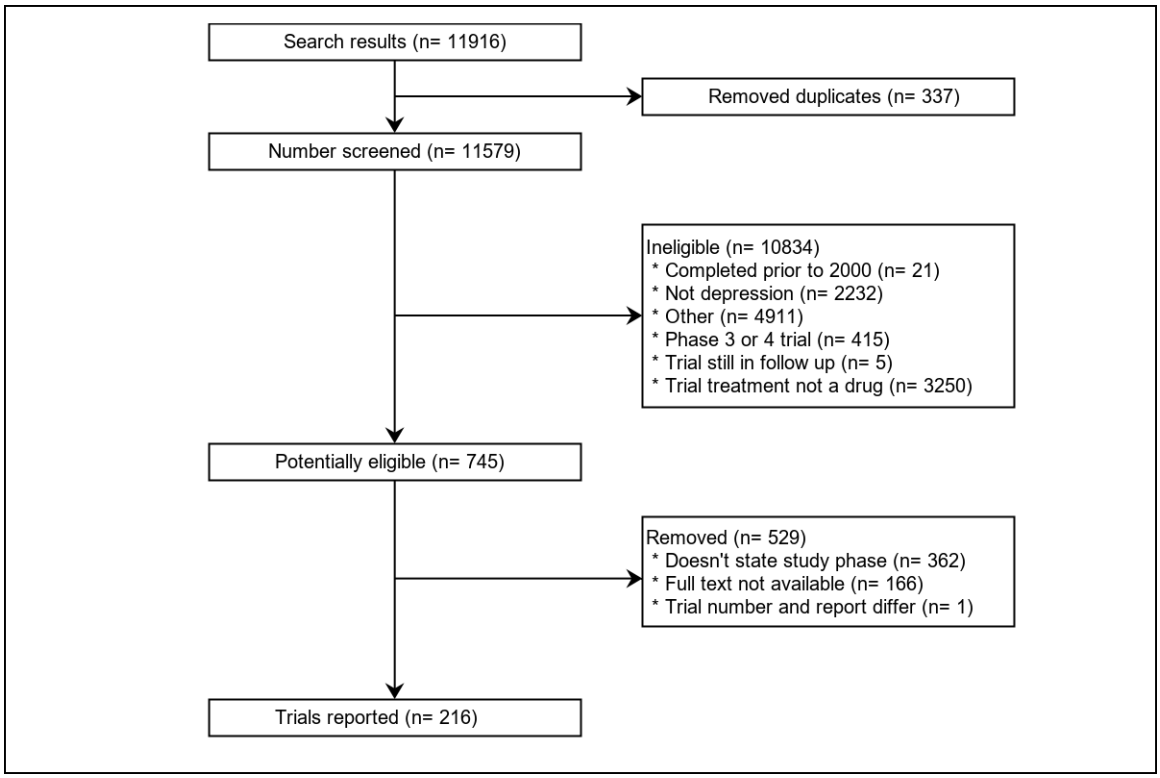

Table 1 Trial summary

	N (%)
Trial design category 1	
Non-randomised	26 (12.0)
Randomised	190 (88.0)
Trial design category 2	
Adaptive*	32 (14.8)
Bayesian	3 (1.4)
Non-bayesian and adaptive design	181 (83.8)
Trial design category 3	
Cross-over	23 (10.6)
Parallel	168 (77.8)
Sequential	1 (0.5)
Single arm	24 (11.1)
Phase of trial	
1	39 (18.1)
1-2	9 (4.2)
2	144 (66.7)
2-3	24 (11.1)
Trial included placebo as a standalone or within a combination treatment	
No	48 (22.2)
Yes	168 (77.8)
Primary outcome	
Efficacy	179 (82.9)
Efficacy and safety	18 (8.3)
Efficacy, safety and tolerability	7 (3.2)
Feasibility	2 (0.9)
Safety	10 (4.6)
Reason trial ended	
Completed	186 (86.1)
Inadequate recruitment due to COVID	1 (0.5)
Not known	2 (0.9)
Terminated/Withdrawn	27 (12.5)
Recruitment challenged but sponsor decided sufficient to demonstrate proof of concept	1 (3.7)
Discrepancies in medication orders	1 (3.7)
Due to data from another study	3 (11.1)
Due to interim	4 (14.8)
Due to pandemic	1 (3.7)
Failure to meet primary endpoint	1 (3.7)
No further/end of funding	4 (14.8)
Not specified	4 (14.8)
Recruitment challenges	2 (7.4)
Side effects/Safety	1 (3.7)
Sponsor decision/Clinical hold by FDA	4 (14.8)
Study team decision	1 (3.7)
Duration of the trial	
1. Less than 1 year	29 (13.4)
2. 1 to 1.5 years	65 (30.1)
3. >1.5 to 2 years	44 (20.4)
4.>2 to 3 years	23 (10.6)
5. >3 to 4 years	20 (9.3)
6. >4 to 5 years	9 (4.2)
7. 5+ years	11 (5.1)

	N (%)
Not known	15 (6.9)
Primary outcome follow up length	
1. Less than 1 day	10 (4.6)
2. Within 1 week	25 (11.6)
3. >1 to 2 weeks	13 (6.0)
4. >2 weeks to 1 month	19 (8.8)
5. >1 to 2 months	106 (49.1)
6. >2 to 4 months	21 (9.7)
7. Beyond 4 months	10 (4.6)
Not known	12 (5.6)

*Adaptive includes those that could be included in both Bayesian and adaptive.

Table 2 Summary of Drugs used in trials included in the cohort

	N (%)
Number of drugs	117
Drug withdrawal information not available for depression	7 (5.98%)
Drug withdrawal not applicable**	60 (51.28%)
Augmentation therapy approved by FDA. NO NICE recommendation. Withdrawn from phase 3 trials as stand alone drug.	1 (1.67%)
Controlled substance	1 (1.67%)
Development discontinued/Drug withdrawn by company	1 (1.67%)
Failed to show efficacy and/or effectiveness in trials	1 (1.67%)
No information provided	6 (10.00%)
Not approved in UK, rejected by FDA in 2019	1 (1.67%)
Not licensed/approved - under investigation/trial	45 (75.04%)
Initial use of drug not for depression	1 (2.22%)
NA*	44 (97.78%)
Not treatment for depression	1 (1.67%)
Probiotic/Nutraceutical/Dietary supplement	3 (5.00%)
Drug not withdrawn	25 (21.37%)
Controlled substance	1 (4.00%)
Not licensed/approved - under investigation/trial	1 (4.00%)
NA*	17 (68.00%)
Only approved in certain countries	6 (24.00%)
Drug withdrawn from development	25 (21.37%)
Development discontinued/Drug withdrawn by company	18 (72.00%)
Cardiovascular concerns (QTc prolongation)	1 (5.56%)
Initial use of drug not for depression	1 (5.56%)
Lack of efficacy/failed to meet primary outcome	7 (38.89%)
NA*	7 (38.89%)
Safety concerns/Lack of efficacy and/or effectiveness	2 (11.11%)
Failed to show efficacy and/or effectiveness in trials	6 (24.00%)
EMA withdrew application for new indication of drug in the treatment of resistant major depression episodes	1 (4.00%)
Benefit didn't outweigh the risk	1 (100.00%)

*NA is provided where no further information is available.**No indication of drug withdrawal or approval which could be withdrawn for the treatment of depression.