**Title:** A prospective cohort study examining the effectiveness of baclofen in the maintenance of abstinence in alcohol use disorder patients attending a joint liver and alcohol treatment clinic

**Short Title:** Effectiveness of baclofen for alcohol use disorder

**Corresponding Author**: Dr Lynn Owens PhD BA Hons Dip HE Cert Ed RN. Nurse Consultant Alcohol Services/Hepatology RLBUHT & Honorary Research Fellow University of Liverpool. Wolfson Centre for Personalised Medicine, Institute of Translational Medicine, The University of Liverpool, UK

Tel. 0151 795 5395

Email: lynno@liv.ac.uk

**Authors:** Dr Lynn Owensa&b , Dr Andrew Thompsonb , Dr Abi Rosec , Professor Sir Ian Gilmoreb Professor Sir Munir Pirmohamedb , Dr Paul Richardsona

aThe Royal Liverpool University Hospital Trust (RLBUHT) & Honorary Research Fellow University of Liverpool. Wolfson Centre for Personalised Medicine, Institute of Translational Medicine, The University of Liverpool, UK

bWolfson Centre for Personalised Medicine, Institute of Translational Medicine, The University of Liverpool, UK

cSenior Lecturer in Psychology, Department of Psychological Sciences. Psychology, The University of Liverpool, Liverpool, UK

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**3193 words** \*excluding abstract and including references

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**Abstract**

**Objective:** Alcohol related liver disease (ARLD) is the leading cause of alcohol-related mortality in the UK. Helping patients with ARLD to stop drinking is an important treatment goal. The aim of this study is to measure the effectiveness of baclofen in maintaining abstinence. **Methods:** A Prospective cohort study Patients with ARLD were commenced on baclofen; the dose was titrated according to tolerability and response up to 30 mg three times daily. Severity of physical dependence and biochemical markers of liver injury were assessed at baseline, 3 and 12 months. **Results:** Length of follow-up differed: Of 219 patients in the original cohort, 186 and 113 were evaluated at 3 and 12 months, respectively. Loss to follow-up was due to death, baclofen non-adherence and failure to attend appointments. Comparison of baseline and 1 year biochemical markers showed significant reductions in GGT (median change = 82.0; 95% CI = -149.0 to -40.0; *P* < 0.0005*),* ALT (-10.5; 95% CI = -16.5 to -5.0; *P* = 0.001) and bilirubin (-4.5; 95% CI = -7.0 to -2.0; *P* < 0.001). The proportion of eligible patients reporting complete abstinence at 3 and 12 months was 55% and 53%, respectively. A significant reduction in alcohol consumption and Severity of Alcohol Dependence Questionnaire score was observed at both follow-up time points. **Conclusion:** Adherence to thebaclofen was good, and it had a positive impact on measures of alcohol consumption. A limitation of our study is its observational nature. Further randomised studies alongside investigation of dosing strategies are required.

**Introduction**

In the last 50 years, the UK has observed a dramatic rise in alcohol consumption with a corresponding increase in alcohol-related disease[1](#_ENREF_1). In particular, the incidence of Alcohol Related Liver Disease (ARLD) has risen sharply, while rates in most other EU countries are declining[2](#_ENREF_2). In England and Wales, 63% of all alcohol-related deaths in 2012 were caused by ARLD, with 16% of these deaths occurring in a relatively young age group (55-59 years)[3](#_ENREF_3). Importantly, all of these deaths are potentially preventable with abstinence from or reduction in alcohol consumption. There is therefore an urgent need to optimise treatment pathways to support individuals with evidence of ARLD to prevent disease progression and associated mortality.

The National Institute for Health and Care Excellence (NICE) have approved several pharmacotherapies (acamprosate, naltrexone and disulfiram) to treat alcohol use disorders (AUD) [4](#_ENREF_4); however both naltrexone and disulfiram are contraindicated in ARLD and data on the safety of acamprosate in the presence of severe hepatic impairment is limited to one study(110). As liver disease is common in AUD patients[5](#_ENREF_5), [6](#_ENREF_6), patients usually receive no treatment[7](#_ENREF_7), or occasionally they may receive psychosocial support alone.

Baclofen is a γ-aminobutyric acid B (GABAB) receptor agonist that has been extensively used as an anti-spasticity agent. More recently however, it has been posited that the stimulation of GABAB receptors by baclofen inhibits the release of the excitatory amino acids, glutamate and aspartate, which reduce the rewarding and/or pleasurable effects of alcohol. Importantly, excretion of baclofen is mainly via the kidneys[8](#_ENREF_8), and it is therefore not contraindicated in patients with liver disease. Thus, baclofen may provide a much needed pharmacological option especially in patients where other pharmacological interventions have failed or liver impairment is present.

Findings from preclinical studies and open-label trials generally support the role of baclofen in the reduction of both alcohol drinking and alcohol-seeking behaviour[9-15](#_ENREF_9). Subsequent randomised, placebo-controlled, clinical trials reported positive results[16](#_ENREF_16), [17](#_ENREF_17). Addolorato and colleagues[17](#_ENREF_17) randomised 84 patients with alcohol dependence and comorbid liver cirrhosis to receive baclofen 30 mg/day or placebo (1:1) for 12 weeks, and reported significantly higher rates of abstinence, a greater number of cumulative days without consuming alcohol, and improved markers of liver injury. However, a US-based trial that recruited 80 patients with DSM-IV criteria for current alcohol dependence was unable to replicate these positive findings[18](#_ENREF_18). Moreover, a French-language meta-analysis concluded that evidence for the efficacy of low dose baclofen in maintaining abstinence was weak [19](#_ENREF_19). The inconsistency in findings presents a position of uncertainty.

Despite RCTs providing gold standard evidence, some of the strict inclusion criteria can often bias samples and limit generalisability of outcomes. For example, trials often exclude patients with underlying disease or require patients to be abstinent for a number of days before joining the study, possibly resulting in a sample that is predisposed to abstinence. Here we aimed to explore the clinical utility of baclofen using an observational dataset from a real world treatment setting. Patients had a diagnosis of ARLD or biochemical evidence of liver damage where previous attempts to remain abstinent using other pharmacotherapies had been unsuccessful, or where approved pharmacotherapies were contraindicated.

**Patients and Methods**

**Design:** We conducted a prospective, cohort study of AUD patients prescribed baclofen with the therapeutic aim of maintaining abstinence. These patients presented with an AUD and either confirmed ARLD or biochemical evidence of liver damage where previous attempts to remain abstinent using other pharmacotherapies had been either unsuccessful or were contraindicated. Patients were commenced on Baclofen 10 mg three times daily (TDS), and the dose titrated according to tolerability and response up to 30 mg TDS. As part of usual clinical care all patients were referred to community services for adjunct psychosocial support.

Consecutive patients were selected with no *a priori* sample size determined.

**Setting:** Patients were recruited from a nurse-led joint hepatology and alcohol treatment clinic in an acute hospital.

**Data Collection:** A prospective dataset was completed by an independent administrator. Information was taken from patient case notes and hospital electronic information systems. This included demographics, co morbidities, alcohol consumption measures (i.e. quantity / frequency utilising Time Line Follow Back(ref form90) methodology and AUDIT[20](#_ENREF_20)), Severity of Alcohol Dependence Questionnaire (SADQ) score[21](#_ENREF_21), biochemical and imaging reports.

**Statistical analysis:** Differences between baseline and three month follow-up, and baseline and 12 month follow-up were analysed. The distribution of the change scores between each pair was assessed for normality. Where the assumption of normality was violated, log transformation was performed. Following this process some data were still not normally distributed and, therefore, Wilcoxon signed rank tests were applied for analysis of the entire dataset without transformation. Effect sizes were calculated using Cohen’s *d* statistic and interpreted according to guidelines[22](#_ENREF_22). Secondary analysis was conducted to explore the effect of the presence of liver disease on drinking outcomes. The significance level was set at *P* < 0.05. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies have been followed in the reporting of our results.

**Results**

Our cohort included a convenience sample of 219 patients, with a median age of 48 years (range: 25-76 years); 112 (51%) were male (Figure 1). Baseline characteristics, including drinking status (i.e. alcohol consumption measures), and liver parameters, are provided in Table 1. Eighty-two (37.5%) patients had cirrhosis; 50 (22.8%) had ARLD but no evidence of cirrhosis indexed radiologically, or by clinical and/or biochemistry assessment. The remaining patients had abnormal liver biochemistry, had been identified as at risk of progression to significant liver disease with continued consumption and had failed previous attempts to maintain abstinence on either acamprosate or naltrexone.

This patient cohort had different lengths of follow-up. To be eligible for follow-up at each time point, patients had to: 1) be alive; and 2) have shown good compliance with the prescribing regime for 1 month. Good compliance was defined using patient self-report; in the previous month, less than two consecutive missed doses or less than six missed doses in total. Of the 219 patients that originally entered the cohort, 190 were eligible for 3 month follow-up, of which 186 (98% of those eligible) attended. At 12 months, 152 were eligible for follow-up, of which 113 (74% of those eligible) attended (Table 4). It is important to note that attrition rates also include 29 patients who failed to take their medicines as prescribed, or failed to attend first follow-up at 1 month, and deaths (*n*=18). Complications of cirrhosis were the primary cause of death for 10 patients. In the remaining 8, the primary causes of death were: 5 non-accidental injury/trauma, 1 cocaine toxicity, 1 alcohol toxicity, and 1 lung cancer.

Comparison of baseline and 1 year biochemical markers showed significant reductions in GGT (*n=*107; median change = -82.0; 95% CI = -149.0 to -40.0; *P* < 0.0005*),* ALT (*n=*106; -10.5 95% CI = -16.5 to -5.0; *P* = 0.001) and bilirubin (*n=*106; -4.5; 95% CI = -7.0 to -2.0; *P* < 0.001*)*. A significant reduction in overall alcohol consumption (*P* < 0.0005) and SADQ score (*P* < 0.0005) was observed at both 3 and 12 month follow-up (Tables 2 & 3). The proportion of patients reporting complete abstinence at 3 and 12 months was 55% and 53%, respectively. Median daily units of alcohol significantly decreased compared to baseline from 25 units per day to 6 and 2 units per day at 3 and 12 months (*P* < 0.0005), respectively. There was no significant difference in rates of abstinence between cirrhotic and non-cirrhotic patients.

Patients with complete AUDIT score data (*n*=105) were categorised for level of risk at each time point according to NICE criteria[23](#_ENREF_23). At baseline no patients were categorised as low risk drinkers, 3 were categorised as increasing risk and 102 as high risk. At 3 month follow-up, 64 patients were categorised as low risk; 10 as increasing risk and 31 as high risk. At 12 month follow-up, 60 patients were categorised as low risk, 14 as increasing risk and 31 as high risk (Figure 2).

In the entire cohort (*n*=219), there was one serious adverse event resulting in discontinuation of baclofen; this was due to development of acute confusion which resolved on cessation of baclofen. Few patients reported adverse effects; for those who did, the effects were minor, short in duration and most commonly included muscle aches and nausea, which resolved spontaneously after 3 to 4 days of taking the medication. In addition, two patients reported stress incontinence. All patients experiencing minor adverse effects chose to continue on their treatment regime.

**Discussion**

Our observational data shows that baclofen was effective in reducing subjective and objective markers of alcohol use and liver biochemistry in a clinical cohort. This cohort was derived from patients with a diagnosis of ARLD or biochemical evidence of liver damage where previous attempts to remain abstinent using other pharmacotherapies had either been unsuccessful, or were contraindicated. This cohort is fairly typical of any patient group attending alcohol services in the UK; it is a group with limited access to pharmacotherapies, previous failed treatment attempts, and at significant risk of disease progression with continued alcohol use[24](#_ENREF_24). Importantly, it is known that continued alcohol consumption in the presence of cirrhosis significantly increases morality rates[25](#_ENREF_25). Moreover, when alcohol-related disease has developed, abstinence can help promote well-being and improve quality of life[26](#_ENREF_26). Therefore, providing well-designed treatment pathways and effective interventions is essential to the future overall health in patients with an AUD.

Our observations are consistent with findings elsewhere in the literature, including a randomised clinical trial by Addolorato et al.[16](#_ENREF_16), which reported significant associations between baclofen administration and improved abstinence rates, cumulative days without consuming alcohol and markers of liver damage. We observed a significant reduction in all of these outcomes between baseline and both 3 and 12 months, coupled with the general improvement in risk categorisation and high rates of retention in treatment (Figure 2). Other observational trials and case studies have also described positive outcomes[15](#_ENREF_15), [27](#_ENREF_27), [28](#_ENREF_28). However, some groups have reported non-superiority of baclofen compared with placebo[18](#_ENREF_18), [29](#_ENREF_29). Several factors have been proposed to explain the lack of concordance between trial results, including differences in adjunctive psychosocial treatment provided and severity of dependence at study entry[30](#_ENREF_30). Furthermore, it has been suggested that severity of liver disease may be an important factor in positive treatment outcome[17](#_ENREF_17), [31](#_ENREF_31). However, we did not observe higher rates of abstinence in cirrhotic compared to non-cirrhotic patients. Although clinical indicators of liver damage improved significantly from baseline demonstrating a global improvement in liver function, a lack of specificity for these markers in relation to alcohol makes interpretation of these findings difficult. Our findings are promising, but this is only preliminary data to support the use of baclofen as adjunctive support in the treatment pathway for this patient cohort, and further work is required.

Our study has several limitations beyond those normally associated with observational data. Firstly, we were unable to provide accurate data for dosing as objective monitoring of adherence is not part of usual clinical care. Secondly, although we observed an improvement in liver biochemistry markers, we were also unable to definitively conclude that these are associated with actual improvements in liver function due to reduced alcohol consumption. Also the use of highly sensitive alcohol consumption markers may increase the accuracy of alcohol drinking measures above that of self-report methods. The use of clinically validated scoring models, such as Childs-Pugh or Model for End-Stage Liver Disease (MELD) is important for categorising disease severity and treatment response, and should be utilised in trials and clinical practice to assess any potential association between liver damage severity and required baclofen dose or treatment effectiveness. This is further compounded by the lack of human laboratory studies that have investigated Baclofen’s action in AUD with co-morbid liver disease. Thirdly, in contrast to previous reports we did not measure the presence or severity of craving and therefore cannot postulate on baclofen’s mechanism of action[32](#_ENREF_32)(refs change). However, a recent evaluation of three commonly used craving scales [Penn Alcohol Craving Scale (PACS), the Alcohol Urge Questionnaire (AUQ) and Items 1-6 of the Obsessive subscale (OBS) of the Obsessive Compulsive Drinking Scale (OCDS)] reported good utility for predicting drinking during treatment, and we agree with the authors that their use should be considered for future studies. Fourth, some patients expressed an interest in treatment with baclofen before it was suggested by the prescriber; such situations may further compound the lack of a placebo arm. Taken together, the lack of placebo arm and lack of craving scales, we are unable to definitively conclude that Baclofen was the active ingredient in alcohol reduction observed. Finally, no objective measure of alcohol consumption such as blood, breath or urine was used, and we were thus reliant on self-reporting, which can introduce bias[33](#_ENREF_33).

Observational data provides an alternative means of assessing clinical effectiveness, particularly in more medically complicated cohorts. Indeed, patients with ARLD represent an under-studied group when considering pharmacotherapies for reducing alcohol consumption. This is especially salient given the association between continued alcohol consumption and the progression of ARLD, and ultimately mortality. The data also provides an indication of the true level of engagement with the treatment pathway. One of the major strengths of this study it that it provides a real world example of interdisciplinary (i.e. hepatology, psychiatry, and hospital alcohol services) working. This approach augments identification of at risk patients, and provides a bespoke pathway of care and treatment in a patient cohort that might otherwise be overlooked. Moreover, we are able to provide outcomes beyond the duration of published RCTs, usually 12 weeks, giving us a more of a longer-term overview of baclofen’s impact.

The repurposing of baclofen may offer an additional therapeutic option but further evidence from well-designed and appropriately controlled trials is required to determine efficacy, treatment response moderators (e.g. genetics and other lifestyle behaviours, such as smokingREF leggio) and dosing profiles. Furthermore, researchers must be willing to utilise a reverse translational approach (“bedside to bench”)[34](#_ENREF_34) to address some of the fundamental questions underlying baclofen’s use in this patient population, including emerging safety concerns e.g.[35](#_ENREF_35), [36](#_ENREF_36). This includes undertaking pharmacokinetic and pharmacodynamic studies in clinically relevant populations (i.e., patients with ARLD) to inform dosing. The range of doses reported in the literature highlight the disparity in prescribing practices. A non-systematic search of the literature reveals that doses range from 5 to 630 mg/d in observational trials, with most RCTs using doses between 30-60 mg/d, with the exception of the BACLAD study which individually titrated patients up to 270 mg/d. Indeed, patients may require different doses to induce an effect, but there is a dearth of evidence to support this process.

In summary, our observational data support the role of a clinical pathway that includes baclofen in promoting alcohol abstinence in patients with liver damage or previous non-response to other pharmacotherapies in a real-world healthcare setting. We hope this study can inform research design to further objectively assess clinical validity and utility. Finally, additional fundamental research investigating the mechanisms of action and correct dosing strategies is required to advance treatment precision.

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**Tables**

**Table 1:** Baseline Characteristics (*n* = 219). Data presented as median (Quartile 1 - Quartile 3)

|  |  |
| --- | --- |
| Age | 48 (Q1=41 - Q3=55) |
| **Gender**  Male  Female | 112  107 |
| AUDIT score | 30 (24-36) |
| SADQ score | 28 (21-33) |
| Quantity of alcohol consumed/daily (UK units) | 25.0 (18-40) |
| **Liver parameters**  ALT  GGT  ALB  BiL | 38 (21-66)  204 (69-465)  42 (37-45)  11 (7-26) |
|  |  |

**Table 2:** 3 month median values and difference between baseline and 3 month scores

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | *Difference between baseline and 3 month follow-up* | | |
| Variable (*n)* | 3 month median (Q1-Q3) | Estimated 95% CI | Wilcoxon *P*-value | Effect size (*d)* |
| AUDIT (186) | 0 (0-22) | -24.0 to -20.0 | < 0.0005 | 0.82 |
| SADQ (186) | 0 (0-16) | -23.0 to -19.0 | < 0.0005 | 0.83 |
| Consumption (186) | 6 (0-15) | -20.0 to -15.5 | < 0.0005 | 0.79 |
| ALT (141) | 28 (20-51) | -15.5 to -3.0 | 0.003 | 0.25 |
| GGT (140) | 102 (45-277) | -131.5 to -48.5 | < 0.0005 | 0.46 |
| ALB (142) | 42 (36-45) | -1.0 to 1.0 | 0.717 | 0.03 |
| BiL (141) | 12 (6-25) | -4.5 to -0.5 | 0.017 | 0.20 |

**Table 3:** 12 month median values and difference between baseline and 12 month scores

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | *Difference between baseline and 12 month follow-up* | | |
| Variable (*n*) | 12 month median (Q1-Q3) | Estimated 95% CI | Wilcoxon *P*-value | Effect size (*d)* |
| AUDIT (113) | 0 (0-20) | -25.0 to -19.0 | < 0.0005 | 0.81 |
| SADQ (113) | 0 (0-17) | -25.0 to -19.5 | < 0.0005 | 0.82 |
| Consumption (111) | 2 (0-13) | -20.0 to -15.0 | < 0.0005 | 0.77 |
| ALT (106) | 29 (20-45) | -16.5 to -5.0 | 0.001 | 0.33 |
| GGT (107) | 103 (44-295) | -149.0 to -40.0 | < 0.0005 | 0.39 |
| ALB (106) | 43(39-45) | -4.1 to 2.0 | 0.051 | 0.19 |
| BiL (106) | 11(7-19) | -7.0 to -2.0 | 0.001 | 0.32 |

**Table 4:** Retention in treatment figures

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Baseline | 3 months | 6 months | 12 months | > 12 months |
| Number of patients expected to attend follow-up | 219 | 190 | 178 | 152 | 122 |
| Number of patients who attended follow-up |  | 186 | 145 | 113 | 86 |
| Percent retained in treatment |  | 98% | 81% | 74% | 70% |
| Number lost to follow-up |  | 4 | 28 | 39 | 36 |

**Figure Legends**

**Figure 1:** Age and sex distribution of the cohort

**Figure 2:** Alcohol consumption risk categorisation at baseline and follow-up for patients with complete data available at each time point (*n* =105). Risk categorisation based on AUDIT score

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Item No** | **Recommendation** | **Where Evidenced** |  |  |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | Title |  |  |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract |  |  |
| **Introduction** | | |  |  |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Introduction |  |  |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Intro P5 |  |  |
| **Methods** | | |  |  |  |
| Study design | 4 | Present key elements of study design early in the paper | Methods P1 |  |  |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods P2 |  |  |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | Methods P1 |  |  |
| (*b*)For matched studies, give matching criteria and number of exposed and unexposed | NA |  |  |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Methods P3 |  |  |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Methods P3 |  |  |
| Bias | 9 | Describe any efforts to address potential sources of bias | NA |  |  |
| Study size | 10 | Explain how the study size was arrived at | Results P1 |  |  |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Methods P4 |  |  |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Methods P4 |  |  |
| (*b*) Describe any methods used to examine subgroups and interactions | NA |  |  |
| (*c*) Explain how missing data were addressed | NA |  |  |
| (*d*) If applicable, explain how loss to follow-up was addressed | Results P2 |  |  |
| (*e*) Describe any sensitivity analyses | NA |  |  |
| **Results** | | |  |  |  |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Results P2  Table 4 |  |  |
| (b) Give reasons for non-participation at each stage | Results P2 |  |  |
| (c) Consider use of a flow diagram | Not used see Table 4 |  |  |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Results P1  Table 1 |  |  |
| (b) Indicate number of participants with missing data for each variable of interest | Results Table 4 |  |  |
| (c) Summarise follow-up time (eg, average and total amount) | Results P2  Table 4 |  |  |
| Outcome data | 15\* | Report numbers of outcome events or summary measures over time | Results P3  P4 and P5  Table 2&3 |  |  |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Results P3 Table 2&3 |  |  |
| (*b*) Report category boundaries when continuous variables were categorized | Results P4 |  |  |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |  |  |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |  |  |
| **Discussion** | | |  |  |  |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion P1&2 |  |  |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion P3 |  |  |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion P6 |  |  |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion P 4&5 |  |  |
| **Other information** | | |  |  |  |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | NA |  |  |