The clinical effectiveness evaluation through an rct, for

The appropriate design of clinical trials, particularly randomized controlled trials (RCT), allows the production ofquality evidence for the assessment of healthcare interventions. Theappropriateness is essentially related with methodological issues, transparency, and the complete descriptions of how studies are conducted sothey can be reproduced and fully assessed. The design of an effectiveness trial, which is thepurpose of this assessment, is usually simpler than the design of efficacytrials, because effectiveness trials tend to accept more wide inclusioncriteria, include flexible regimens, and allow participants to accept or rejectthe interventions offered to them. Typically, these trials evaluate effective interventionsprovided to heterogeneous participants under ordinary clinical circumstances. The current recommendations for the design of a clinicaleffectiveness evaluation through an RCT, for a novel lifestyle interventionincluding motivational interviewing, activity pacing and aerobic exercise forpeople complaining of long-standing low back pain (LBP), considered severalreference from the literature, particularly the CONsolidated Standards OfReporting Trials (CONSORT) statement (Schulz, 2010) and the SPIRIT 2013checklist (Chan, 2013). These two standardsare consensual and generally accepted for planning such trials.

Recommendations: Trial design, e. g. individual patient versus cluster RCT.

4 The choice of comparator 5 The method of randomisation and allocation concealment 6 The choice of primary outcome measure. 7 Methods to promote blinding. 8 Methods of recruitment 9 Methods to maximise retention. 10 · Trial design, e. g. individual patient versus

clusterRCTFor the purpose of the required study, a comprehensivecohort study design might be ideal (multicenter, pragmatic, single-blind, parallel-group, non-inferiority), comparing a novel lifestyle intervention andstandard of care (usual physiotherapy care) for people with long-standing lowback pain. The main reasons are the following: o Thedesign allows to recruit all patients fulfilling the clinical eligibilitycriteria regardless to their consent to randomization; o Mustbe performed an assessment of external validity by comparing the randomizedstudy sample to the population of patients who met the eligibility criteria butdid not consent to randomization;
o Shouldprioritize random allocation of treatment against patient preferences. Thisshould avoid subversion bias.

In this type of studies, the individual will knowin which arm is included;
o Thisdesign avoids the risk of massive drop outs due to consent previous torandomization, which the opposite could lead to bias; o Typeof pragmatic trial, which includes individuals who do not consent to berandomized, reducing selection bias and improving generalizability of results; o Thereis no need to fully understand the concept of randomization by the individuals, which avoids additional anxiety and promotes confidence between patient andclinicians; o Avoidsexpectations and resentful demoralization. Nevertheless, there are some issues, such asinformation denial of trial options prior to randomization and a denial ofpatient choice between interventions, which is not a major issue due to thefact that all individuals will receive care (standard or novel); Whynot other designs? Not needed multiple RCTs over time, so cohort multipleRCT is not necessary, since the population will be randomized for each arm(standard or novel care); A

cluster design wouldn’t be recommended, because itis more important to have a baseline population, rather than a randomization oftime, place, or clinicians. This methodology could also lead to lessstatistical significant conclusions and loss of allocation concealment, whichis fundamental to prevent randomization bias.

This design could be interest if, for instance, the purpose was to assess effectiveness of the novel interventionperformed in a different primary care unit, or delivered by a different type ofhealth professional. Explanatory trials, on the opposite of pragmatictrials, assess if an intervention has an effect under optimal conditions, whilepragmatic trials evaluate effectiveness of an intervention in real-lifeconditions, which is more appropriate for this purpose. For this purpose is not ideal to receive boththreatments (novel and standard care) in random sequences (crossover orfactorial trials), neither clustering, as previously mentioned. Parallel-group(each participant is randomly assigned to a group, and all the participants inthe group receive the novel intervention or standard care) is the recommendeddesign. A standard clinical RCT design could result inmeasures of clinical effectiveness, but there is a risk of low recruitmentrates, poor generalizability and low external validity. · The choice of comparator The purpose is to assess clinical effectiveness of anovel intervention, which means there is a comparator (current standard care)to the novel care. The estimated effect of intervention should clearlydistinguish between standard and novel care, for a similar baseline population. The choice of the comparator must be related to thetrial population, and local context of practice and decision-making.

The potential comparators should rely on alltechnically feasible, acceptable, and relevant alternatives for the purpose ofcare. In the current case, for people complaining of long-standing low backpain. In this particular situation, the comparator should bebased on noninvasive pharmacologic and nonpharmacologic treatments for low backpain, since the intervention is nonpharmacological and noninvasive.

The suggested comparator should be Exercise Therapy, because it is classified as recommended in the NICE recommendations REF? https://www. nice. org. uk/guidance/ng59/resources/low-back-pain-and-sciatica-in-over-16s-assessment-and-management-pdf-1837521693637and American Guidelines REFhttp://annals. org/aim/fullarticle/2603228/noninvasive-treatments-acute-subacute-chronic-low-back-pain-clinical-practice. Exercise Theraphy already proved, with moderate-quality evidence, to have smallimprovements when compared with no exercise and with usual care in a systematicreview for chronic low back pain REF 2: http://www. bprclinrheum. com/article/S1521-6942(10)00003-3/fulltext.

Since there is no evidence that one particular typeof exercise therapy is clearly more effective than others, the Exercise Therapyshould include the most frequent type of exercise plan, or a mix of commonexercise plans. REF. ref.

DOI: http://dx. doi. org/10. 1016/j. berh. 2010.

01. 002. For this comparator, a non-inferiority RCT would fitthe purpose of assessing clinical effectiveness for the novel intervention. An alternative

could be a comparison with usual care. In this case, probably a superiority RCT might be more appropriate to assessclinical effectiveness.

Nevertheless, usual care might consist in a mix ofinterventions, and an appropriate identification of what might be the usualcare in a particular context should be identified. Other alternatives, according to the ClinicalGuidelines Committee of the American College of Physicians, could be multidisciplinaryrehabilitation, acupuncture, or mindfulness-based stress reduction, since allof them have proved a moderate reduction in short-term pain intensity withmoderate-quality evidence. Nevertheless, these options are not recommended byNICE REF? https://www. nice. org. uk/guidance/ng59/resources/low-back-pain-and-sciatica-in-over-16s-assessment-and-management-pdf-1837521693637. Other recommended pathway treatments such aspharmacological and psychological are not suitable for the purpose of thisstudy, since the clinical effectiveness of the novel intervention is not yetproven.

The first step should be to prove the clinical effectiveness among thesame type of treatments in order to include the novel intervention in thetreatment pathway. Comparator should address the appropriateness, inorder to ensure no overestimated effectiveness of the novel intervention. · The methodBM1 of randomisation and allocation concealment If the standard of care consist of only one type ofphysiotherapy care, then the trial should be randomized through an equalassignment of 1: 1 in a 2-arm RCT (novel intervention-arm and control-arm). The selection of patients should be based in clearinclusion and exclusion criteria, in order to ensure concealment of allocation. It is essential that the allocation is not known, knowable, or

guessable priorto recruitment. Random allocation to the novel intervention or comparatorgroups will occur after confirmation of eligibility and baseline assessment. The method used should be a stratified blockrandomization. The stratification should be by region, since it’s a multicentertrial and it is expected some heterogeneity between regions.

The blocking willallow to assess whether the severity of low back pain over the treatment armsconduces to a difference in response. The most suitable method should be a randomizationafter consent, due to a risk of subversion (only opened when the patient hasconsented) and bias (higher possibility of drop outs due to the fact thatindividuals will not undergo the novel lifestyle plan). Selection bias isavoided through this method, because allocation is purely by chance, and thechance of getting the observed effects is completely and absolutely free fromany confounding effects.

After the selection of patients (inclusion andexclusion criteria), the randomized allocation can be processed either by localrandomization using a pre-prepared sequence or by remote randomization. The mostsuitable way could be a remote allocation, blinded and performed using acomputer-generated random allocation schedule operated by a remote researcher. The allocation of participants should then be concealed by using sequentiallynumbered, sealed and opaque envelopes. These envelopes, sealed usingtamper-proof security tape and impermeable to intense light, should besequentially numbered and opened sequentially only after participant detailsare written on the envelope. After randomization, patients would be included in thetrial-arm (novel lifestyle intervention) and control-arm (standard ofphysiotherapy care). During this process, all the

participants, including theones who drop out after randomization, should be recorded.

This process guarantees compliance. This processshould be clear in the report, to provide minimal criteria judgement ofadequate concealment of allocation, complying with Cochrane systematic reviewrecommendations REF and the concealment mechanism from SPIRIT statementREF.. Group allocation Allocation will be.

Source: https://www. ncbi. nlm. nih. gov/pmc/articles/PMC4717625/pdf/12891_2015_Article_852. pdfCochrane: · The choiceBM2 of primary outcome measureThe primary outcome should aim to evaluate theclinical effectiveness of a novel lifestyle intervention, based on whetherindividuals in the novel lifestyle arm report significant improvement, comparing with those allocated for current standard of physiotherapy care.

Since the novel lifestyle intervention includesmotivational interviewing, activity pacing and aerobic exercise for peoplecomplaining of long-standing low back pain, and the study purpose is to assessclinical effectiveness, an appropriate measure of quality of life (patientrelated outcome measure – PROM), that produces numerical information thatdescribes the well-being of patients, should be identified that answers, atleast, eight concepts: appropriateness, acceptability, feasibility, validity, reliability, responsiveness, precision and interpretability. In this particular situation, a multi-dimensional andgeneric PROM measure is recommended to measure pain disability as primaryoutcome and there are robust and validated PROM measures

available. There’s noneed to develop an entire new PROM measure. When checking the PROM instruments available, Roland-MorrisDisability Questionnaire (RMDQ) could be recommended as an example BM3 to better measure outcomes for effectivenessevaluation, since is adequate to measure health changes due to novel care, itcontains 24 items relating to a range of functions commonly affected by LBP, allows to assess overall effectiveness through a score, and its generally usedfor non-specific low back pain quality of life measures REF https://www. ncbi. nlm. nih. gov/pmc/articles/PMC5077121/.

Since there are some limitations with RMDQ, particularlyceiling effect (at some point, the variation of scores doesn’t reflect acondition improvement or declining), Ref: https://www. ncbi. nlm. nih.

gov/pubmed/29154811, the Modified Von Korff Scale would also berecommended as complementary and valid for low back pain, because it assessesdisability and its impact on daily activities, recreation, and ability to workRef: A multicentred randomised controlled trial of a primary care-based cognitivebehavioural…. Also, the Aberdeen Back Pain Scale, ÖrebroMusculoskeletal Screening Questionnaire (OMSQ or OMSQ-12), OsteoporosisFunctional Disability Questionnaire, Psychosocial Functioning Questionnaire forPatients with Low Back Pain, Quebec Back Pain Disability Scale, and Oswestrypain disability index could also be used. Other non-specific back pain PROMscould also be used, such as Brief Pain Inventory, Short Form 36 physicalfunctioning subscale and McGill present pain index. These are appropriate because they answer the questionof the study; they are acceptable, because it only requires a few time andnon-invasive

procedures; they are feasible, easy to process and requires fewtime from professionals and participants; they are valid, since they werealready tested and published; they are reliable, because the validity processalready showed internal validity and consistency; they are responsive, sinceallows to detects changes over time in the quality of life for patients withLBP; they are precise since the scores result from several dimensions of care; and the interpretability is high, because the score result is associated with adegree of health state associated with patient preferences.

The suggestion of these PROMs doesn’t mean that literatureshould not be consulted to detect other possible PROM measures, as well as theconsultation of ePROVIDE resources. Depending on the setting where the studywill be used for decision-making, the authority guidelines should be consulted, as well as patients and clinicians, for the same reason. · Methods BM4 to promote blinding Blindness is recommended in order to avoid thesubversion risk (e. g.

the allocation of the next envelope, if not blinded, could be performed only when a suitable patient appears, which is notdesirable). Blinding of the treating physiotherapists andparticipants will not be possible because they will know the intervention armto which they have been allocated. The blinding should be performed for outcomeassessment, and is achieved if neither patients nor those involved in the trialhave any means to discover which arm a patient is in.

When considering the risk of bias from lack ofblinding of outcome assessment it is important to consider specificallywho is assessing the

outcome, and the risk of bias in the outcomeassessment (considering how subjective or objective an outcome is). Questionnaires at all time points will beself-completed by the patient. A valid method could be to inform patients notto tell outcome assessor the treatment they received and fill the questionnairein a centralized research facility, where the assessor had no contact with theintervention procedure. In this case, a letter should be sent to participantsbefore any assessment stating that they should make no mention of theirintervention. Ref.

methods: http://journals. plos. org/plosmedicine/article? id= 10. 1371/journal. pmed. 0030425In this way, blinding will be achieved by having anindependent blinded assessor performing the follow-up assessments after 6 and12 months.

The blinded assessor will not be treating any of the participants, nor be aware of their group allocation. The statistician conducting the primary data analysiswill also be blinded to group allocation. Authors should consider to group outcomes with similarrisks of bias.

This method follows the CONSORT and SPIRIT statements, and The Cochrane Collaboration’s tool for assessing risk of bias. ref? · MethodsBM5 of recruitment Participants meeting the eligibility criteria previouslydefined will be recruited. Potential participants can be identified throughsearching general practice records, and from direct referrals from generalpractitioners. Treating physiotherapists will screen (all) potentialparticipants from the outpatient clinics, and inform them about the study. Potential participants interested in participating inthe study will receive an information statement

and be referred to the researchteam. Patients with chronic LBP who meet the inclusioncriteria will be invited to participate in the trial. A research assistant willdiscuss the study and offer participation to those who meet the inclusioncriteria, including a participation fee.

If they agree to participate a signedconsent form will be recorded and baseline data will be collected. Source: https://www. ncbi.

nlm. nih. gov/pmc/articles/PMC4717625/pdf/12891_2015_Article_852. pdfEach potential participant goes through an eligibilitycheck. Telephone reminders to non-respondents, opt-outprocedures requiring potential participants to contact the research team ifthey do not want to be contacted about the trial, and the financial incentiveswith the trial invitation are the key features for recruiting REF.

. Ref. https://www.

journalslibrary. nihr. ac. uk/hta/hta11480#/abstractThe patients will provide written informed consentprior to randomisation. The participants providing written consent areconsecutively included and randomized. ? http://dx. doi.

org/10. 1136/bmjopen-2012-002360 Fonte: Methods toimprove recruitment t oRCT: Cochrane ... · Methods BM6 to maximise retention The comprehensive cohort study design is useful toimprove recruitment rates, because it does not exclude from the RCTparticipants with strong preferences. At the beginning, patient preferences are elicitedbefore randomisation occurs, and the study design recruits all patients thatare eligible regardless of their consent to randomisation.

Those who do notconsent to randomisation are kept in the study but their treatment choice ismade based on preference. Patients who consent are randomized to the twotreatment choices. A method to maximize retention should addressparticipants motivation and the maintenance of the participants and siteclinicians engaged with the trial. It is proven that providing incentives canimprove retention REF.

. Loss of participants must not exceed 5%. In the worstcase scenario, 20% or greater loss of participants might threaten the trialvalidity. Despite the possibility of solving some issues by statisticalmethods, the risk of bias will remain.

For this particular study, it is recommended to:- Providemonetary incentives to the participants who consent to randomization and remainin the attributed arm (no more than 10 euros, so it won't be perceived ascoercion for data). The incentive should be given after the reception of afully answered questionnaire.- Keepthe questionnaire short. Nevertheless, this aspect should not be considered asa priority since there is no sufficient evidence that it would provide anincrease of responses;- Contactpeople before sending the questionnaires. Non-monetary incentives are not proven to be effectiveways of maximizing retention, because they don't increase response ratesREF..

This method might increase retention, providinggreater generalizability, validity and reliability to the trial results. Source: " strategies to improve retention in randomizedtrials: a Cochrane systematic review and meta-analysis", Brueton, et al. (http://dx. doi. org/10. 1136/bmjopen-2013-

003821) BM1DONE BM2DONE BM3The Roland Morris Questionnaire(RMQ) is the most widely used measure of LBP disability in primary-care trials.

itcontains 24 items relating to a range of functions commonly affected by LBP. 102It takes less than 5 minutes to complete. It has good reliability101 but thereare concerns that it does not conform to many of the assumptions that underpinits use in statistical analysis (scaling and normality of distribution). Datafrom the Oxfordshire Low Back Pain Trial suggested that it had a marked ceilingeffect, failing to capture important clinical information on improvement inparticipants with subacute or chronic LBP attending NHS physiotherapy. It hasbeen shown to be differentially sensitive at low, mid and high ranges, with(not unsurprisingly) better sensitivity in the middle range.

108, 109 In the lowto mid range, the RMQ is less sensitive to within-group changes than theAberdeen Low Back Pain Score, but better at detecting between-groupdifferences. 101 TheModified Von Korff Scale (MVK)103 assesses two dimensions – pain and disabilityassociated with back pain in the last 4 weeks. It is made up of six items, eachof which is scored on a scale of 0 (no pain/disability) to 10 (worstpain/disability). The first three of these items relate to disability and askabout how back pain interferes with (1) daily activity, (2) recreation and (3)ability to work.

The last questions relate to pain and assess the (1) worstpain, (2) average pain and (3) rating of back pain today. The questionnaire wasadministered at baseline, 3, 6 and 12 months. BM4DONE BM5DONE BM6DONE