Background information on selected variables

This section highlights important variables and details how they were defined, how they were changed throughout the review process, issues observed through data extraction, and similarity to variables used in other reviews regarding eligibility criteria.

For each selected variable we report:

-variable name

-variable description from codebook and from detailed guide to extraction

-notes, including changes made to variable, issues with variable observed through data extraction, and similarity to variables used in other reviews regarding eligibility criteria

Variable name
sample_cc_targeted

Variable description

Is the trial selection targeting individuals with multiple chronic conditions?	◯ No ◯ Yes, individuals with a specific set of chronic conditions ◯ Yes, individuals with multiple chronic conditions, regardless of conditions ◯ Yes, individuals with any combination of chronic conditions within a specific set of conditions

Is the trial selection targeting individuals with multiple chronic conditions?
No
Participants are selected based on their diagnosis of only one chronic condition
Ex: All individuals in the study sample must have diabetes
Yes, individuals with a specific set of chronic conditions
Participants are selected based on their diagnosis of a specified set of 2 or more chronic conditions
Ex: All individuals in the study sample must have diabetes and hypertension
Yes, individuals with multiple chronic conditions, regardless of conditions
Participants are selected based on their diagnosis of 2 or more chronic conditions, regardless of specific combination of conditions
Ex: All individuals in the study sample must have 2 chronic conditions
Yes, individuals with any combination of chronic conditions within a specific set of conditions
Participants are selected based on their diagnosis of 2 or more chronic conditions, within a specified set of chronic conditions. Multiple combinations are possible.
Ex: All individuals in the study sample must have 2 or more of the following chronic conditions: depression, hypertension, diabetes, arthritis, and chronic heart failure.

Notes

This variable was intended to identify if trials targeted participants with MCC. Originally this was a yes/no question however we ultimately added additional options as we came across different types of eligibility criteria. By expanding the "yes" category into multiple options we are able to better to describe how broad or narrow the eligibility criteria for MCC were. A similar variable was used in du Vaure.[1]

Variable name
cc_list

Variable description

Is the trial selection targeting individuals with one condition from a specific set of chronic conditions?	◯ No ◯ Yes

Is the trial selection targeting individuals with one condition from a specific set of chronic conditions?
Please note that these trials may include people with multiple chronic conditions, but do not require patients to have multiple chronic conditions.

No, all participants in the study have the same chronic condition
Yes, participants in the study must have at least one chronic condition from a specified set of chronic conditions.
Ex: Each participant must have one of the following chronic conditions: diabetes, hypertension or depression.

Notes

This variable was added to distinguish between studies that were focused on one specific condition and those that did not target MCC yet targeted a variety of conditions. A similar variable was not seen in other reviews.

Variable name
elig_criteria_behav
elig_behav

Variable description

Were any behavioral factors/conditions are used as inclusion or exclusion criteria?	◯ No ◯ Yes
Which of the following behavioral factors/conditions were reported as eligibility criteria?	☐ Alcohol use ☐ Smoking or tobacco use ☐ Other substance use ☐ Physical activity ☐ Diet ☐ Weight

Were any behavioral factors/conditions are used as inclusion or exclusion criteria?
Yes if any of the eligibility criteria is behaviorally based.
This includes substance use (alcohol, smoking, or other), level of physical activity, diet or weight.

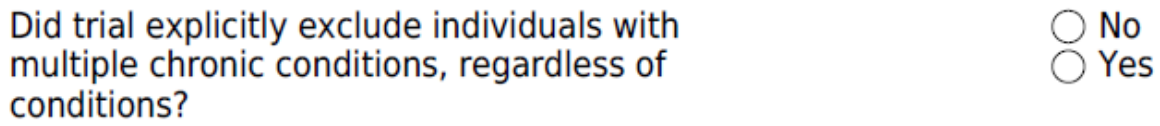
Which of the following behavioral factors/conditions were reported as eligibility criteria?
Check all that apply
Alcohol use
Levels of alcohol consumption
If alcohol abuse disorder is an eligibility criteria (all participants have the condition), do not select this option
Ex: Participants must not drink more than 1 serving of alcohol per day
Smoking or tobacco use
Smoking status or use of tobacco products
Ex: Participants must be non-smokers, participants must not have used tobacco products in the past 10 years
Other substance use
Use of other controlled substances besides alcohol and tobacco
If substance abuse disorder is an inclusion criteria (all participants have the condition), do not select this option
Ex: Participants must not have used cocaine in their lifetime
Physical activity
Levels of physical activity or sedentary behavior
This does not include criteria based on an individual's ability to perform physical activity (such

as “Must be able to walk without assistance”)
Ex: Participants must not currently exercise more than 1 time per week
Diet
Any criteria based on the content of the diet, frequency of meals or other eating behaviors
Ex: Participants must currently eat 3 meals per day, participants must not have an eating disorder
Weight
BMI restrictions, weight or obesity status
Ex: BMI must be below 30, participants must not be overweight, participants must be obese

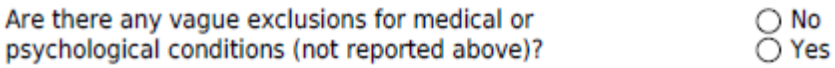
Notes
This variable was created to identify risk behaviors that may be used in eligibility criteria as criteria based on these may make trials more or less likely to include MCC. An unanticipated issue with this variable was studies could either exclude participants who engaged in higher risk behaviors/condition or exclude those with lower risk behaviors/conditions, and the variable does not currently distinguish between these. However, in addition we extracted the exact wording of the relevant eligibility criteria so there is further opportunity to address this. A similar variable was not seen in other reviews.

Variable names
mcc_exclusion; elig_vague; condition_exclusion

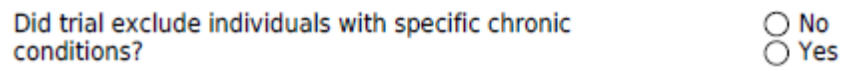
Variable descriptions



Did trial explicitly exclude individuals with multiple chronic conditions, regardless of conditions?
Yes if individuals with more than one chronic condition (regardless of condition) were excluded from the trial



Are there any vague exclusions for medical or psychological conditions (not reported above)?
Yes if there is any vague mention of exclusions due to medical or mental illness that is not captured in the form above.
These are broad exclusions not specific to chronic conditions that may have implications for excluding individuals with chronic conditions
Examples: Excludes patients with any “co-occuring medical condition”, “serious medical conditions”, “psychological illness”, “mental disorder”, etc.



Did trial exclude individuals with specific chronic conditions?

This does not include the chronic condition(s) shared by all participants- do not use this question to describe limitations on inclusion of the targeted chronic condition(s) (which is reported in Intervention Details)
No
Did not report exclusion of individuals specifically based on any of the 20 chronic conditions, even if individuals were excluded on the basis of having more than one chronic condition, but no specific condition is named
Yes
Individuals were excluded from the trial on the basis of having one or more of the 20 chronic conditions, which is specifically named or determined by diagnostic criteria for the condition
Ex: Individuals with depression were excluded from the trial or individuals with systolic blood pressure >140 were excluded from the trial

Notes
These variables form the framework of eligibility criteria that we developed. They were reworked several times throughout the data collection process and based on what we saw in the trials these three categories of MCC exclusion (general, vague, specific) were created to distinguish between the different ways in which MCC may have been excluded. This allowed us to identify that vague exclusions are common and may result in MCC being excluded very often from trials.

Jadad[2] distinguishes specific and general exclusions (called implicit and explicit in their review) and Boyd[3] considers terms for comorbidities as compared to condition names, however the categorization exclusion criteria related to MCC as specific, general, or vague is unique to our review.

Type of exclusion	**Definition**	**Examples**
Specific	exclusion of individual conditions by name or diagnostic criteria	Type 2 diabetes, HbA1c > 7%
General	exclusion of MCC by general term	chronic disease, additional comorbidities
Vague	exclusion criteria that is likely to result in exclusion of specific conditions, but do not provide enough information to determine which conditions would be excluded	serious medical problems, acute medical complications, unstable medical conditions, mental illness, too ill

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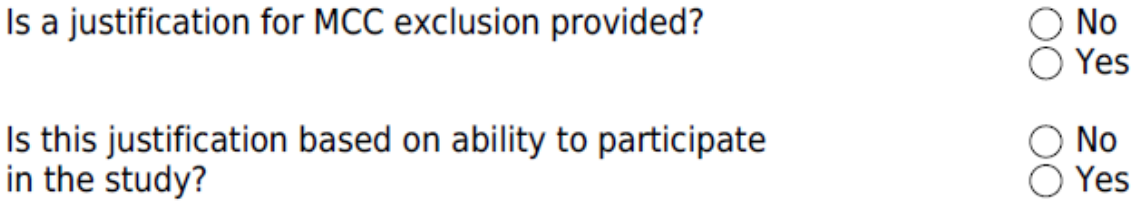
Variable names
mcc_exclusion_just; mcc_ability; vague_ability; condition_ability

Variable descriptions



Is a justification for MCC exclusion provided? (mcc_exclusion_just)
No- did not provide rationale for excluding individuals with MCC
Yes- did provide rationale for excluding individuals with MCC

Is this justification based on ability to participate in the study? (mcc_ability)
Yes if exclusion is based on the patient's physical or mental capacity to participate in the study

Is this exclusion based on ability to participate in the study? (vague_ability)
Yes if exclusion is based on the patient's physical or mental capacity to participate in the study
Ex: Excludes for any illness that limits the patient's ability to partake in the intervention

Did trial exclude individuals with specific chronic conditions?	◯ No ◯ Yes
Is this exclusion based on ability to participate in the study?	◯ No ◯ Yes

Is this exclusion based on ability to participate in the study? (condition_ability)
Yes if exclusion is based on the patient's physical or mental capacity to participate in the study
Ex: Excludes individuals with dementia due to inability to complete intervention components

Notes

For each type of exclusion (general, specific, vague) we indicated if the exclusion was justified (yes/no) and if so, was it justified by an inability to participate in the intervention. We added the "inability to participate" option because we observed that this was a common justification given, although rarely was it explained how it was determined that the condition would prevent the individual from performing or participating in the intervention. Van Spall[4] considers justification of exclusion criteria in their review.

Variable name
exclusion_15

Variable description

Is exclusion of individuals with Hypertension narrowed?	☐ No ☐ Yes- narrowed by type ☐ Yes- narrowed by severity ☐ Yes- narrowed by onset ☐ Yes- narrowed by other specification

Is exclusion of individuals with [SELECTED CHRONIC CONDITION] narrowed?
No- all individuals with this broadly defined chronic condition were excluded from the study
Yes- only individuals with a specific type and/or severity of this chronic condition were excluded from the study

Is this condition narrowed by type, severity, onset or other specifications?

No
The chronic condition common to all study participants is broadly defined as one of the 20 chronic conditions above.
Yes- narrowed by type
The chronic condition common to all study participants is a more specific type of one of the 20 chronic conditions above.
Example of cancer narrowed by type: All individuals in the study sample have breast cancer.
Yes- narrowed by severity
The chronic condition common to all study participants is a specific severity of one of the 20 chronic conditions above.
Example of cancer narrowed by severity: All individuals in the study sample have stage III cancer.
Yes- narrowed by onset
The chronic condition common to all study participants is narrowed by date of diagnosis or duration of illness.
Example: All individuals in the study sample were diagnosed within the past 5 years.
Yes- narrowed by other specification
The chronic condition common to all study participants is a more specific version of one of the 20 chronic conditions above, but is narrowed by a method other than type, severity, or onset.

Notes
We added this variable to allow for distinguishing between studies that exclude participants with any form a condition and studies that exclude only a certain version of that condition. For example, studies may exclude anyone with hypertension, or they may only exclude those with extremely high blood pressure. We felt that this was an important distinction to make, as studies may exclude the very ill only, which would result in a more generalizable trial than those that exclude the moderately ill as well. However, a potential issue with this variable is that as it is used now we are not able to distinguish between those that exclude the sicker and those that exclude the less sick. However, there is a free text variable associated with this that contains the exact wording of the exclusion so that we are able to explore this in the future. This variable was not seen in other reviews, however Boyd[3] explicitly included exclusions for conditions whether they were for a severe version of the condition or a narrow version.

Variable names
age_restrict
age_restric_type
max_age

Variable descriptions

Were there any age restrictions for trial participants (aside from 18 years or older)?	◯ No ◯ Yes
What type of age exclusion?	☐ Minimum Age ☐ Maximum Age
Excluded those above age:	_____

Were there any age restrictions for trial participants (aside from 18 years or older)?
No- the only age restriction for the trial is that participants had to be at least 18 years old
Yes- additional age restrictions were used, which further limited eligibility

Notes
These variables allow us to see if MCC are likely to have been excluded through the use of age restrictions. Jadad,[2] Boyd,[3] Zulman,[5] and Van Spall[4] considered age restrictions in their reviews.

Variable names
mcc_reported; mcc_infer

Variable descriptions

Are multiple chronic conditions included in the participant characteristics?	◯ No ◯ Yes
Could the inclusion of individuals with multiple chronic conditions be inferred?	◯ No ◯ Yes

Are multiple chronic conditions included in the participant characteristics?
This may be reported in the Subjects section or in Table 1
Yes if article reported one of the following:
Number of study participants who also had another chronic condition not necessary for inclusion
Mean number of chronic conditions per participant
Charlson Comorbidity index mean and standard deviation
Ex: In a trial where all patients have diabetes, Table 1 lists the percentage of patients with hypertension
Ex: In a trial where all patients have diabetes and hypertension, Table 1 lists the number of patients with depression.

Can the inclusion of individuals with multiple chronic conditions be inferred?
Yes if participant characteristics inferring the presence of multiple chronic conditions were reported
Ex: A trial with cancer as a selection criterion lists the number of participants taking anti-hypertensives. It can be inferred that these individuals have multiple chronic conditions because they have both cancer and hypertension.

Notes
During extraction we identified that we were potentially missing relevant information by only looking for terms for MCC or specific condition names. It could sometimes be inferred that MCC were included even though it was never stated. There were two ways we saw this most often. The first way was through a description of medication taken by participants. A trial may not report presence of hypertension explicitly but report number of patients on anti-hypertensives. This trial would be classified as being able to infer the inclusion of MCC. The other way we saw this information presented would be through description of the participants using a score that measures symptoms of one of our chronic conditions. This was most often seen as a score for depression, such as the PHQ-9. The trial could present statistics regarding PHQ-9 score among participants that would allow us to infer that depression was present in the population, for example a mean score above the threshold for diagnosis or a range of scores that went above the threshold for diagnosis. A trial presenting information in this way would be classified as being able to infer presence of MCC. A similar variable distinguishing between the explicit inclusion of MCC and the inferred inclusion of MCC was not seen in other reviews.

Variable name

mcc_reported_spec

Variable description

Is this description general or condition specific?	☐ General ☐ Condition Specific

Is this description general or condition specific?
Check all that apply
General- study broadly described a group of participants with multiple chronic conditions (ex: # of participants with comorbid conditions)
Condition Specific- study specifically described group(s) of participants with certain chronic condition(s) (ex: # of participants with hypertension)

Notes
The amount and quality of information reported relating to MCC presence in these trials was more variable than we expected. Throughout the review we found that information was often presented based on individual conditions rather than overall measures of comorbidity. This variable was added to distinguish between the way MCC presence was reported. We found that trials could report MCC presence generally by reporting a broad measure of MCC such as number of participants with comorbid conditions or mean number of chronic conditions or they could report presence of specific conditions, such as number of participants with hypertension. When MCC information was presented only through the condition specific information, it was usually difficult to know how the conditions were distributed among participants. For example, if 40% of participants had condition A and 30% of participants had condition B it was not possible to know how many participants had both conditions. A similar variable was not seen in previous reviews.

Variable names
bias_rand_seq; bias_alloc; bias_performance; bias_detection; bias_attrition; bias_report

Variable descriptions

Random sequence generation (selection bias)	◯ Low Risk ◯ High Risk ◯ Unclear Risk
Allocation concealment (selection bias)	◯ Low Risk ◯ High Risk ◯ Unclear Risk
Blinding of participants and personnel (performance bias)	◯ Low Risk ◯ High Risk ◯ Unclear Risk
Blinding of outcome assessment (detection bias)	◯ Low Risk ◯ High Risk ◯ Unclear Risk
Incomplete outcome data (attrition bias)	◯ Low Risk ◯ High Risk ◯ Unclear Risk
Selective outcome reporting (reporting bias)	◯ Low Risk ◯ High Risk ◯ Unclear Risk

Random sequence generation (selection bias)
Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
Low Risk criteria:
The investigators describe a random component in the sequence generation process such as:
- Referring to a random number table;
- Using a computer random number generator;
- Coin tossing;
- Shuffling cards or envelopes;
- Throwing dice;
- Drawing of lots;
- Minimization*

*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
High Risk criteria:
The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:
- Sequence generated by odd or even date of birth;
- Sequence generated by some rule based on date (or day) of admission;
- Sequence generated by some rule based on hospital or clinic record number.

Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:
- Allocation by judgement of the clinician;

Allocation by preference of the participant;
Allocation based on the results of a laboratory test or a series of tests;
Allocation by availability of the intervention.

Unclear Risk criteria:

Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

Allocation concealment (selection bias)

Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment.

Low Risk criteria:

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

Central allocation (including telephone, web-based and pharmacy-controlled randomization);
Sequentially numbered drug containers of identical appearance;
Sequentially numbered, opaque, sealed envelopes.

High Risk criteria:

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

Using an open random allocation schedule (e.g. a list of random numbers);
Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);
Alternation or rotation;
Date of birth;
Case record number;
Any other explicitly unconcealed procedure.

Unclear Risk criteria:

Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding of participants and personnel (performance bias)

Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.

Low Risk criteria:

Any one of the following:

No blinding or incomplete blinding, but the reader judges that the outcome is not likely to be influenced by lack of blinding;
Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

High Risk criteria:

Any one of the following:

No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;
Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Unclear Risk criteria:

Any one of the following:

Insufficient information to permit judgement of 'Low risk' or 'High risk';

The study did not address this outcome.

Blinding of outcome assessment (detection bias)
Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
Low Risk criteria:
Any one of the following:
- No blinding of outcome assessment, but the reader judges that the outcome measurement is not likely to be influenced by lack of blinding;
- Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

High Risk criteria:
Any one of the following:
- No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;
- Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Unclear Risk criteria:
Any one of the following:
- Insufficient information to permit judgement of 'Low risk' or 'High risk';

The study did not address this outcome.

Incomplete outcome data (attrition bias)
Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
Low Risk criteria:
Any one of the following:
- No missing outcome data;
- Missing outcome data is clearly explained
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- Missing data have been imputed using appropriate methods.

High Risk criteria:
Any one of the following:
- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- Clearly missing outcome data with no explanation provided
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;

For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;
Potentially inappropriate application of simple imputation.

Unclear Risk criteria:
Any one of the following:
Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided);
Cannot determine whether data is missing
The study did not address this outcome.

Selective outcome reporting (reporting bias)
State how the possibility of selective outcome reporting was examined by the review authors, and what was found.
Low Risk criteria:
Any of the following:
The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High Risk criteria:
Any one of the following:
Not all of the study's pre-specified primary outcomes have been reported;
One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear Risk criteria:
Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.

Notes
These variable make up our risk of bias assessment and are taken from the Cochrane Collaboration Risk of Bias score. We modified several of the items to fit our review. Although the scale is designed to assess basic aspects of RCT design, we found that this information was often not reported and the 'unclear risk' category for each of these variables was assigned much more than anticipated. Although other reviews considered study quality,[4] no other reviews used this scale.

Variable name
sub_analysis_comorbid

Variable description

Were comorbidities used in a subgroup analysis? ◯ No ◯ Yes

Is comorbidity information considered in analysis?
Primary outcomes were compared between individuals with and without comorbidities

Notes
Originally we had several variables we were extracting related to the data analysis of the trial such as whether the subgroup analysis was planned or unplanned, was a difference found, was the difference favorable for the MCC subgroup, was an interaction term used to test for effect modification, etc. However we ultimately found that MCC information was considered in analysis so rarely that it was necessary to create one yes/no variable to indicate if information was considered in analysis. This variable is similar to ones seen in reviews by Boyd[3] and Zulman.[5]

1. du Vaure CB, Dechartres A, Battin C, Ravaud P, Boutron I. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials. gov: a systematic review of registration details. *BMJ open.* 2016;6(9):e012265.
2. Jadad AR, To MJ, Emara M, Jones J. Consideration of multiple chronic diseases in randomized controlled trials. *JAMA: the journal of the American Medical Association.* 2011;306(24):2670-2672.
3. Boyd CM, Vollenweider D, Puhan MA. Informing evidence-based decision-making for patients with comorbidity: availability of necessary information in clinical trials for chronic diseases. *PloS one.* 2012;7(8):e41601.
4. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *Jama.* Mar 21 2007;297(11):1233-1240.
5. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *Journal of general internal medicine.* 2011;26(7):783-790.