Abstract

Objective

Clinical trials are often conducted in different stages which can lead to differences in how they are reported or cited. This can lead to difficulties when developing search strategies for systematic reviews. The objective of this study is to determine if established RCT methodological search filters should include terms for trial phase.

Study design and setting:
Case study. A search filter for trial phase (the P3 filter) was developed and its sensitivity, efficiency and value was determined when compared to two established RCT methodological search filters in the year 2015.

- improved sensitivity was determined where the P3 filter identified studies missed by either of the established filters;
- efficiency was determined by the number needed to read; and
- The Cochrane risk of bias tool was used to determine study quality as a proxy for value.

Results
Both established filters missed studies. One missed one RCT and four follow-up RCT studies. The other missed one RCT and five follow-up RCT studies. Study quality was unclear.

Conclusions
Established RCT literature search filters may miss studies where trial phase is reported instead of terms for study design or randomisation. The P3 filter can be incorporated to improve sensitivity.

Background

Clinical trials are often conducted in different stages which can lead to differences in how they are reported or cited. This can lead to difficulties when developing search strategies for systematic reviews. For example, a randomised controlled trial (RCT) may be referred to as a phase III (or phase 3) study, with no mention of study design (i.e. controlled trial) or the method of randomisation used. The authors of this

report have observed this in both original reports of studies and in follow-up analysis. As such we aimed to determine whether established RCT methodological search filters should include terms for trial phase.

Specific reporting guidance has been developed to aid study authors when reporting RCT. Consolidated Standards of Reporting Trials (CONSORT) guidance recommends identifying the report of a trial by using the term 'trial' in the title of the study (CONSORT guidance 1a) and by using a structured summary in the abstract to report aspects of trial design and study methodology (CONSORT guidance 1b) (1). The use of CONSORT has been linked to improving the effectiveness and efficiency of literature searching for RCT (1-4). CONSORT reporting guidance works hand-in-hand with corresponding advances in biomedical databases (namely: the introduction of indexing terms for studies reporting RCT into MEDLINE and Embase (5), the creation of Cochrane's CENTRAL register of controlled clinical trials (6, 7), and the retrospective 're-tagging' of relevant study records in MEDLINE and Embase (8-10)) which has developed the process of literature searching in intervention effectiveness systematic reviews and it has paved the way for the use of study design methodological search filters to identify studies reporting RCTs (11-15).

A study design literature search filter is a pre-determined (and preferably validated) list of study design or methodological search terms likely to appear in the title, abstract or bibliographic indexing of relevant studies (16-21). Search filters used to identify RCT and studies reporting RCT focus on key methodological aspects commonly found in trials, such as 'random' to indicate randomisation, 'trial' to indicate that a trial has taken place, or 'placebo' to indicate a comparator or non-active treatment. The presence of these terms in a study design literature search filter then match with the report of the study in the title, abstract and bibliographic indexing terms, to ensure that relevant studies are identified for screening.

Where study authors do not adhere to CONSORT reporting guidance, for example by labelling a study by trial phase not study design, it may affect the operating characteristics of study design methodological search filters for RCTs. This is potentially problematic for study identification in health technology assessment (HTA), and other reviews of intervention effectiveness, such as Cochrane systematic reviews, which prioritise RCT as their primary unit of analysis (22). It could mean that potentially relevant studies are missed in literature searching where study design methodological search filters are used, and that studies and study data are omitted in systematic reviews, leading to incomplete estimates of intervention effectiveness.

Study aim and objectives

The aim of this study was to test the hypothesis that including search terms for study phase in addition to study design or methodological search terms improves the sensitivity of RCT methodological search filters.

The objectives of this study were:

(i) to develop a set of search terms to identify studies reporting by trial phase. These search terms will be represented as a search filter called the P3 filter, where P represents study phase and 3 indicates the trial phase;

(ii) to determine if the use of the P3 filter improves the sensitivity of two established RCT methodological search filters (i.e. does the inclusion of the P3 filter identify relevant studies missed by two RCT methodological search filters); and

(iii) to determine the efficiency of study identification and value of any studies identified by the P3 filter missed by the two established RCT methodological search filters.

Methods

The methods set out below relate to the three objectives enumerated above.

Objective i: developing the P3 filter

A search filter to identify studies reporting by trial phase (but not identifying by study design) was subjectively derived based on the authors experience and led by the indexing structure of the bibliographic database MEDLINE (Ovid interface) (23).

This search filter is set out in Figure 1 in the form of a search narrative (24, 25). Search narratives aim to define the conceptual and contextual purpose of literature searches (24). In this instance, it explains the decision-making behind the development of the P3 search filter.

Figure 1 The P3 filter

Conceptual purpose: The purpose of this search filter is to identify studies that report RCT by trial phase (i.e. Phase 3) but which do not report study design terminology (i.e. trial or controlled or randomisation). We aim that this filter be combined with established methodological search filters for RCTs to increase sensitivity in study identification. Database: MEDLINE Host: Ovid Data Parameters: 1946 to October 23, 2018 Date Searched: Friday October 26th 2018 Searched: CC PRESS Checked by: JVC	
Search strategy	**Search Narrative**
1 clinical trial, phase iii/ (14273)	Line one represents MeSH (controlled indexing language for the database MEDLINE) for phase III clinical trials. The number reported in parentheses (14273) is the number of studies identified by this specific search line.

2 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw. (59575)	Line two represents free-text terminology for trial phase. Free-text terminology means that the words identified in parenthesis in line two will be searched in the title (ti), abstract (ab), or author generated keywords (kw). Any incidence of any of these terms will be identified in the fields specified.
3 1 or 2 (64807)	The MeSH and free-text terminology are combined at line 3 using the Boolean connector OR. This means that either or both items will be identified.

The search filter was checked using the PRESS checklist by the study co-authors (26, 27). No issues or amendments were identified.

Objective ii: to determine if the use of the P3 filter improves the sensitivity of two well-known RCT methodological search filters

Two established RCT methodological search filters were selected by the study authors from the Information Specialist Sub-Group (ISSG) Search Filters resource (28). The methodological search filters chosen were:

i) **Strategy 1: The Cochrane Highly Sensitive Search Strategies (HSSS).** The HSSS were written and developed by Carol Lefebvre and were first published in 1994 (8, 22) (Figure 2). The HSSS filters were selected based on their wide-spread use for Cochrane systematic reviews, and in other types of systematic reviews. The sensitivity and precision-maximizing version of the HSSS was selected following the guidance of the Cochrane Handbook since the sensitivity-maximizing version of the HSSS, produced an unmanageable number of studies to process (22);

ii) **Strategy 2: The Royle and Waugh search filter (BRSS)** (4) The 'Brief RCT search strategy' (BRSS) was developed by Royle and Waugh and published in 2005 (4) (Figure 2). Royle and Waugh argued that the Cochrane Collaboration had undertaken the exhaustive work to identify and report trials in CENTRAL, and CONSORT reporting guidance has since improved the visibility of trials generally, that a simple search of MEDLINE and Embase using the filter Random$.af., and a search of CENTRAL, is now sufficient to identify to RCT for systematic reviews in most cases (4). This filter was selected based upon its ease of use (one search line compared with 10 in the HSSS) and the strength of its operating characteristics as reported in the validation study by the authors (4).

Figure 2 The Cochrane HSSS and Royle and Waugh BRSS search filter

Strategy 1: The Cochrane HSSS RCT literature search filter
1. randomized controlled trial.pt.

2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9

Ovid search syntax
.pt. denotes a Publication Type term
.ab. denotes search in abstract
.ti. detonates search in title
.shj. denotes subject heading
.sh. denotes a Medical Subject Heading (MeSH) term
.ti. denotes a word in the title

Strategy 2: Royle and Waugh BRSS RCT literature search filter
1. Random$.af.

Ovid search syntax
.af. denotes all fields
$ denotes truncation

To determine any improvement in sensitivity, a systematic search and double-screening of studies identified was undertaken in MEDLINE (Ovid interface).

Study identification
Rather than select a population, intervention, or topic area to focus on, which would limit the scope for evaluation to a specific context, a year was selected at random from the last twenty completed years (1997-2017). This provides a broader scope, across a range of clinical areas, to test the study objectives. Each of the last completed years (i.e. 1997-2017) were entered into Microsoft Excel sequentially and then randomised. 2015 was the year reported in the top cell after randomisation.

The database used for testing was MEDLINE (Ovid interface). The following search logic was used to complete the search:

1. HSSS search filter
2. The P3 search filter
3. 2 NOT 1
4. Limit 3 to 2015

This process was repeated for the BRSS filter. The results of both searches were kept separate for screening.

Screening

All studies were independently screened by two reviewers using the following criteria:

Title/abstract screening

- Include (1): study reported a phase 3 RCT or a follow-up report of a RCT or a posthoc analysis of a RCT;
- Include (2): if uncertainty around inclusion criteria 1 exists.
- Exclude: study reported was a cohort study, case series, study conducted on animals, or the study reported pooled analysis of two or more RCT.

At full-text screening, the screening decision was binary: include if the study was a phase 3 RCT and exclude if not. The following definition of an RCT was used:

'A published or unpublished report of a study in which a number of individuals (or other units) are prospectively randomised and allocated to 1 or 2 (or more) groups to test a specific technology, treatment or device' (22, 29).

Objective iii: to determine the value of any studies identified by the P3 filter and missed by the RCT methodological search filters.

An increase in sensitivity would be represented by the identification of any study fulfilling inclusion criteria at full-text which was missed by either of the established RCT study design methodological search filters. To contextualise sensitivity, the efficiency of the P3 filter, and the potential value of any relevant studies identified was determined.

Efficiency

The Number Needed to Read (NNR) was used to contextualise any improvement in sensitivity relative to any additional work-load required to identify additional relevant studies. The NNR indicates the number of studies a researcher would need to read to identify a relevant study. It is calculated as 1/precision, where precision is the proportion of retrieved articles that are eligible (21).

Value

The value of any missed studies was also measured. The Cochrane Risk of Bias tool was used to determine study quality as a proxy for study value (30). All studies fulfilling inclusion criteria at full-text were independently appraised by the lead reviewer and checked for accuracy by a second reviewer.

Results

Literature searching was undertaken on April 7th 2018 and there were no reported problems with the bibliographic database MEDLINE (Ovid interface) on this day. PRISMA flow-charts are reported in supplementary material for each search filter.

The HSSS: objective ii

The P3 search filter identified 2023 studies not identified by the HSSS. Of these, 1983 were discarded at title/abstract as not fulfilling inclusion criteria (inter-rater

reliability for screening was 98%) and 40 studies were taken to full text screening. Five studies fulfilled inclusion criteria at full-text: one RCT (31) and four follow-up studies (32-35). Table 1 reports study characteristics and the reason why studies were missed by the HSSS.

The BRSS: objective ii

The P3 search filter identified 2256 studies not identified by the BRSS. Of these, 2219 were discarded at title/abstract as not fulfilling the inclusion criteria (inter-rater reliability for screening was 98.6%) and 37 studies were taken to full text screening. Six studies fulfilled inclusion criteria at full-text: one RCT (31) and five follow-up studies (32, 34-37). Table 1 reports study characteristics and the reason why studies were missed by the BRSS.

Sensitivity, efficiency and value: and objective iii

One study reporting an RCT was missed by both the HSSS and BRSS filter (30). Nasr et al (31) was missed as it did not report either study design terms or terms for randomisation in the title or abstract and the study was not indexed as an RCT. We therefore find that the P3 search filter did improve the sensitivity of the both the HSSS and BRSS RCT methodological search filters. As reported above, in terms of efficiency, the NNR for HSSS was 1/2023 and 1/2256 for the BRSS filter.

Study quality was used as a proxy to interpret what value a missed study might add to a systematic review. The findings of the assessment of Risk of Bias are reported in Figure 3 for all studies. There is an unclear risk of bias for the majority of the domains assessed. Overall, it is unclear what the likely value would be of the RCT and follow-up studies should they have been missed in a systematic review.

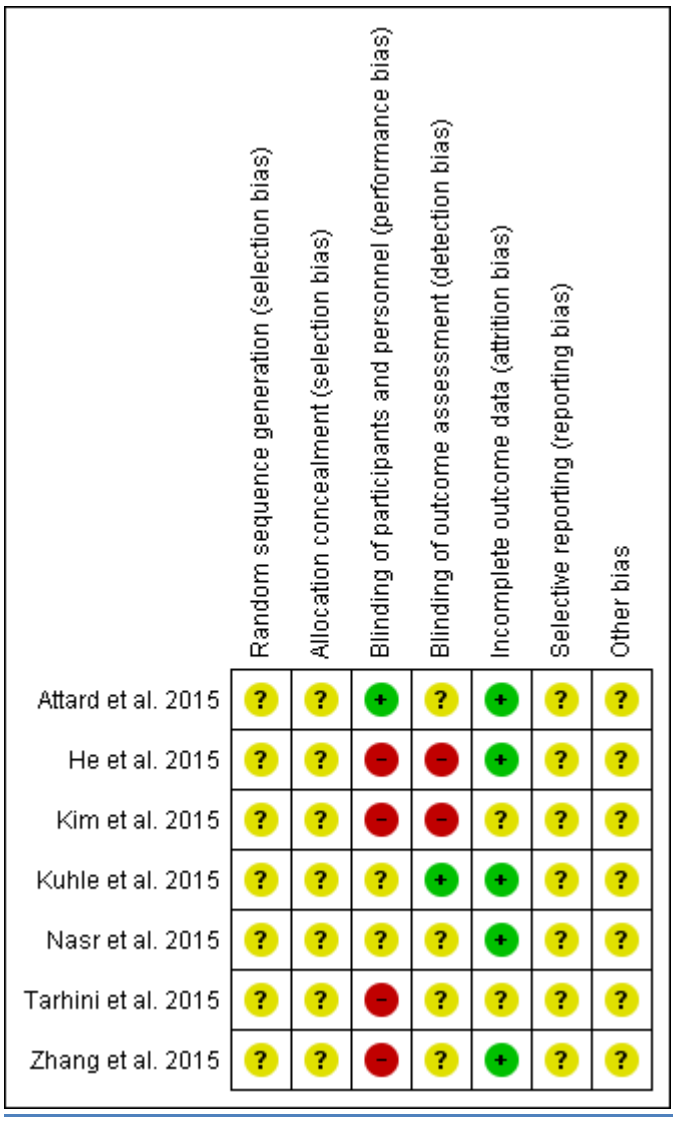
Table 1 Studies identified by the P 3 filter

Study	Study identified by filters				Characteristics	Reason why missed
	BRSS	BRSS + P3	HSSS	HSSS+ P3		
Attard et al 2015 (32)	X	√	X	√	Follow up or new analysis of previously reported trial	No mention of randomisation or study design in title or abstract. Not indexed as an RCT.
He et al. 2015 (33)	√	√	X	√	Follow up or new analysis of previously reported trial	Indexed as 'Randomized controlled Trials as Topic' and not as Randomized Controlled Trial.mp. (line 1 of the HSSS). No reference to placebo or randomisation in the abstract (lines 4 and 6) and no reference to trial in the title (line 7).
Kim et al. 2015 (34)	X	√	X	√	Follow up or new analysis of previously reported trial	No study indexing. No mention of randomisation or study design in the title or abstract.
Kuhle et al 2015 (36)	X	√	√	√	Follow up or new analysis of previously reported trial [a]	No mentioned of randomisation in the title or abstract.
Nasr et al. 2015 (31)	X	√	X	√	Randomised trial	No mention of randomisation or study design in the title or abstract. Not indexed as an RCT.
Tarhini et al. 2015 (35)	X	√	X	√	Follow up or new analysis of previously reported trial [a]	No mentioned of randomisation or study design in the title or abstract.
Zhang et al. 2015 (37)	X	√	√	√	Follow up or new analysis of previously reported trial	No mentioned of randomisation or study design in the title or abstract.

Notes: a, study included at FT, no evidence of randomisation in the paper but trial registry identified the study was.

Key: BRSS: The Royle and Waugh Brief RCT search strategy, HSSS, The Cochrane Highly Sensitive Search Strategies.

Figure 3 Cochrane risk of bias for included studies



Discussion

This study demonstrated that two established study design methodological search filters for RCT missed one RCT and six follow-up RCT studies where study authors reported the phase of the trial (i.e. phase iii or phase 3) and not study design terminology (i.e. RCT).

What does our finding mean?

The results of this study demonstrate that the HSSS and BRSS RCT filters may not identify all potentially relevant studies where study authors neglect to use study design terminology, or identify the process of randomisation, following CONSORT reporting guidance. It would seem likely that this finding applies to other study design methodological search filters for RCT which also do not include search terms for study phase.

Is this an important finding?

In intervention effectiveness systematic reviews, yes. To generate a reliable estimate of intervention effect it is important to identify all relevant studies in the literature search and include them in a systematic review (38). Researchers have explored and demonstrated this by including and excluding studies from statistical meta-analysis, finding a change in the point estimate where relevant studies were omitted from meta-analysis (38). This finding has generally been used to argue for the importance of comprehensive literature searches for systematic reviews of intervention effectiveness (39). Understood in this specific context, missing any relevant, yet potentially accessible study, would be considered a limitation of study identification in the review process.

Six of the studies identified uniquely by the P3 filter were follow-up studies. The purpose of literature searching in intervention effectiveness reviews is to identify all relevant studies and study data and so this finding reflects a potentially important finding in addition to the identification of an original study report. Follow-up studies often provide further or additional outcome data which aids interpretation of the effectiveness of the intervention. This can be of particular importance in certain clinical situations, in determining the long-term safety or effectiveness of new treatments, for example. In the currently controversial area of mesh surgery, one-year effectiveness data (40) is not nearly as crucial as long-term complication data, which would only be reported in follow up publications (e.g. (41)).

Bibliographic database searching is indicated as the primary method of study identification in leading systematic guidance documents (39). Identifying these follow-up studies in the bibliographic database searches – as opposed to later in the process of a systematic review, through citation chasing included studies, for instance – allows for a more complete assessment of study data at an earlier stage of review. This may be more important than perceived, as citation chasing included studies is a step in the review process often not conducted, particularly when rapid reviews are undertaken (42).

What are the implications of this finding?

The findings that are presented are based on one case study and an example based on one year. Whilst these limitations are acknowledged, the principal implication of our findings are that the two established RCT methodological search filters examined in this case study, missed studies because study authors did not follow CONSORT reporting guidance. To the best of our knowledge, other RCT methodological search filters do not typically include terms that would cover the phase of the trial either.

The implication of our findings suggests that the P3 search filter should be incorporated alongside the study design methodological search filters examined in this case study, if a comprehensive or exhaustive identification of studies is the aim of literature searching. It is important to state, clearly, that the P3 filter should be used in addition to, and not in place of, any established RCT methodological search filters.

Including the P3 filter will increase the number of studies to screen. It is not, however, anticipated to make a substantial difference overall, since literature searches for intervention effectiveness systematic reviews commonly use the PICO mnemonic to structure their literature searches (39). The NNR reported in this study (HSSS: 1/2023 and BRSS 1/2256) likely overstates the number of studies to screen because we have not used population or intervention search terms in this experimental case study. By way of example, comparing the HSSS and BRSS with and without the P3 filter by repeating the MEDLINE (Ovid interface) literature search from a recently published multiple technology assessment (43) found that the P3 filter increased the number of studies to screen by four for the HSSS and two in the BRSS. Such a small rise in the number of studies to screen, when compared with the potential to identify studies potentially missed (as we demonstrate here), would seem to confirm the claims we make for efficiency, effectiveness and value in this case study. We include the search strategy for this worked example in the on-line material.

This study aimed to test a hypothesis of increased sensitivity in literature searching for RCT and infer if high-or low-quality studies were identified by the P3 but missed by the HSSS/BRSS. Incorporating an evaluation of study quality was an attempt to contextualise our findings, moving the interpretation of our results beyond purely quantitative outcomes (i.e. the P3 filter identified a greater number of relevant studies than the HSSS/BRSS) to explain why they matter and what they mean. It is likely that researchers may be asked to screen additional studies if the P3 filter is used and this increase in resources (which we anticipate to be minor) needs to be suitably justified.

The quality of the studies uniquely identified is unclear which does not help interpret the value of missing them through the HSSS/BRSS or identifying them via the P3. Six of the seven studies were follow-up studies which referred to previously published papers where more details could be found on the methods. It is therefore likely that greater clarity on the risk of bias from each study could have been gathered through combining the assessment with these papers too. It was decided that, given the purpose of the risk of bias was to understand the value of the missed papers, that the risk of bias should only be conducted on the paper identified rather than all linked published papers as we would have done in a full systematic review.

This is a potential limitation since it only demonstrates the quality of the specific studies identified and not the effect of the study in the context of synthesis or meta-analysis. We are unable to determine the 'true value' of the studies as a contribution to synthesis as has been done elsewhere (38, 44) but extending the analysis of literature search evaluation beyond 'more studies were identified' to explain 'why this matters' is an important if yet imperfect area of development (45).

The findings of this study would suggest that study authors, particularly those reporting trials, may benefit from a reminder of CONSORT guidance. This may take the form of greater diligence from editors and peer reviewers to comment on and

ensure that CONSORT reporting guidance is followed by study authors. The findings identified in this study are not a criticism of the RCT methodological search filters but rather an identification of issues in study reporting to which a solution is required in intervention effectiveness systematic reviews.

The implications identified are not limited to literature searching using RCT methodological search filters. Study authors whom have sought to test text mining or machine learning for trials identify similar issues with studies that do not follow CONSORT guidance (c.f. (46)). Moreover, clear reporting of methodological terms in the title and abstract may improve the effectiveness and efficiency of study identification in other areas of research, such as identifying studies reporting diagnostic or prognostic test evaluation.

Study limitations

We have conducted a robust and novel study; however, some limitations should be acknowledged.

The P_3 filter reported in this case study is subjectively derived from the authors experience and led by the indexing structure of the bibliographic MEDLINE (Ovid Interface). Further work could usefully be developed to further test and evaluate the P_3 search filter objectively, through creation of a 'gold standard' test set of phase 3 trial papers and comparing the retrieval performance of the HSSS and BRSS compared to the P_3 filter. Such work would extend the preliminary analysis and findings presented in this study, to develop a validated methodological search filter. Royle and Waugh suggest that the BRSS should be used in Embase in addition to searches of MEDLINE and CENTRAL (4). The Cochrane Handbook suggests that Embase be searched where resources permit for the HSSS (22). The work reported in this study was undertaken without any specific funding to support it; accordingly, our attention was focused on study identification in MEDLINE. The findings of this study appear to suggest that studies which report by trial phase and not methodological terms for study design may be missed by study design methodological search filters. Since the focus is on the free-text terminology reported by study authors, it would seem unlikely that repeating this analysis in Embase would alter the findings of this study, but we acknowledge this limitation.

A limitation to the uptake of using the P_3 filter, most particularly when it comes to Cochrane reviews, is that Cochrane currently recommend the use of the HSSS methodological search filter only. Therefore, a search that included the P_3 search, would not strictly be acceptable for a Cochrane review.

It is possible that the studies missed by RCT methodological search filters may have been identified by other non-database search methods in a systematic review. It is important to acknowledge that literature searching is a holistic approach to study identification, drawing on a variety of search methods, to identify relevant studies and study data for review. It is, however, also acknowledged that many systematic reviews, particularly when conducted under tight resource and time constraints, rely entirely on the database search and do not conduct further levels of searching.

There is also some potential advantage to identifying studies and study data in the early stages of review as opposed to later and by non-database search methods.

Conclusions

Researchers who aim to identify studies reporting RCT should be aware that established RCT methodological search filters may miss studies where the terminology of study design or process of randomisation is not reported in the study.

Researchers may, accordingly, be advised to incorporate search terms for trial phase in addition to using RCT methodological search filters to ensure the comprehensiveness of their literature searches. An initial suggestion for a search filter to identify Phase III trials is presented in this study which can easily be adapted to include or exclude other phases and incorporated for use alongside existing RCT methodological search filters.

Authors of studies reporting RCT would be reminded of the importance of following CONSORT reporting guidance when reporting RCT since this relates to the effective and efficient identification of their studies.

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This paper extends the work presented there. The screening was entirely re-done in 2018 and 100% double-screened at title/abstract and full text. Study quality was also determined. The literature searching, screening and quality appraisal were undertaken by CC and JVC. PC acted as third reviewer. CC wrote the first draft of the manuscript. All authors reviewed and approved the manuscript prior to submission. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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