Mental Health Clinical Advisory Group

Research Methods

House Bill 2300 (2017) and Senate Bill 138 (2019)

- The MHCAG will develop evidence-based algorithms for mental health treatments
- Algorithms for mental health drugs must consider the following:
    - Efficacy and Safety
    - Cost
    - Patient-specific factors
- Algorithms for mental health drugs must be based on:
    - Peer-reviewed medical literature
    - Observational studies
    - Health economic analyses
    - Input from patients and physicians
    - Any other information that the MHCAG deems appropriate
- The MHCAG makes recommendations to the OHA Pharmacy and Therapeutics Committee on:
    - Implementation of evidence-based treatment algorithms
    - Changes to any preferred drug list used by OHA
    - Practice guidelines for the treatment of mental health disorders with mental health drugs
- All agencies of state government are directed to assist the MHCAG in the performance of their duties
- Mental health drugs in this context include prescription drugs within Standard Therapeutic Classes 07 (ataractics, tranquilizers) and 11 (psychostimulants, antidepressants), lamotrigine and divalproex

The MHCAG Mission

Develop high-quality, clinically relevant behavioral health treatment guidance documents based on best available evidence, patient values and addressing current health inequities.

The Research Methods

1. Develop specific clinical research questions
    a. Determines scope, defined and focused
    b. Identify PICOS
        i. Population: populations based on demographic characteristics and clinical diagnoses; include marginalized populations based on race, ethnicity and other factors in which evidence would help address existing health inequities
        ii. Intervention: the specific treatment that needs to be reviewed
        iii. Comparator: fair and reasonable treatment comparison
        iv. Outcomes: clinically important outcomes assessed at appropriate timeframe
        v. Setting: provider type and level of care
2. Identify high quality systematic reviews from the following preferred sources:

i. Drug Use Research & Management Program (DURM) at Oregon State University College of Pharmacy
ii. Drug Effectiveness Research Project (DERP) at the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University
iii. Agency for Healthcare Research and Quality (AHRQ)
iv. Canadian Agency for Drugs and Technologies in Health (CADTH)
v. National Institute for Clinical Excellence (NICE)
vi. BMJ Clinical Evidence
vii. U.S. Department of Veterans Affairs/Department of Defense (VA/DoD)

3. Identify other relevant literature from biomedical databases using appropriate search criteria
    a. Databases include: MEDLINE (Ovid, PubMed), Epistemonikos, ACCESSSS, NCBI Bookshelf
4. The MHCAG relies primarily on high quality systematic reviews and randomized controlled trials (RCT) to assess efficacy and harms treatment outcomes.
    a. High-quality systematic reviews meet AMSTAR II criteria (see **Appendix 1**).
    b. The internal validity of RCTs is assessed using a modified Cochrane Risk of Bias tool (see **Appendix 2**).
    c. FDA analyses, if available, may also be considered to complement published studies
    d. Research will be based on hierarchy of evidence:
        i. Systematic reviews (high quality)
        ii. Randomized, controlled trial (high quality)
        iii. Large, longitudinal, controlled cohort studies (especially for safety outcomes)
        iv. Poorer quality systematic reviews and controlled trials
        v. Case-control studies
        vi. Cross-sectional studies
        vii. Unpublished controlled studies (e.g., posters, abstracts, presentations, etc.)
        viii. Non-controlled studies
            1. Surveys
            2. Case series
            3. Case reports
    e. Large observational studies and systematic reviews of observational studies can be used to evaluate long-term safety outcomes
    f. Expert opinion may be considered to answer very specific research questions that cannot be answered by controlled studies
    g. Studies which evaluate clinically meaningful outcomes will be emphasized over studies which evaluate proxies for these outcome (surrogate endpoints)
        i. Mortality
        ii. Morbidity
        iii. Quality of life
        iv. Function
        v. Symptoms
    h. Studies which evaluate U.S. populations, in particular populations from historically marginalized U.S. communities and groups (BIPOC, houseless, Medicaid, etc.) will also be emphasized
5. The MHCAG will utilize high-quality clinical practice guidelines to complement outcomes data found in the primary literature
    a. Systematically developed with high standards using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach
    b. Provides transparent process using evidence and other data to make recommendations
    c. Thoroughly researched and cited using multiple relevant references

d. Meets the modified AGREE II-GRS criteria (see **Appendix 3**)

6. GRADE the evidence
    a. GRADE (Grading of Recommendations, Assessment, Development and Evaluations)
        i. A transparent, systematic framework for developing and presenting summaries of evidence
        ii. Quality of evidence is applied to each outcome researched, based on the clinical research questions
    b. Grade certainty ratings:

Certainty	Interpretation
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The true effect is probably close to the estimated effect
High	The true effect is similar to the estimated effect

    c. By necessity there is a considerable amount of subjectivity in each GRADE
    d. Assess 5 factors across the individual studies that are sufficiently large enough to affect certainty in an outcome and downgrade an initial certainty GRADE of High (RCT) or an initial certainty GRADE of Low (observational studies) one level lower
        i. Risk of bias: allocation concealment, blinding, attrition
        ii. Imprecision: 95% confidence intervals encompass a reasonable range
        iii. Inconsistency: effect estimate similar across studies
        iv. Indirectness: applicability of patients, intervention, outcomes and setting
        v. Publication bias: missing evidence, study funding
    e. Certainty may be rated up for: large magnitude of effect; obvious dose-response gradient; when all residual confounding would decrease the magnitude of effect (in situations with an effect); or at the majority judgment of MHCAG when significant clinical experience with the treatment and patient preferences are considered.

APPENDIX 1. Methods to Assess Quality of Systematic Reviews.

The AMSTAR II was developed and shown to be a reliable measurement tool to assess the methodological quality of systematic reviews. There are 16 components addressed in the tool below, and questions can be scored in one of four ways: “Yes”, “Partial Yes”, “No”, or “Not Applicable”.

High quality systematic reviews do not contain a “fatal flaw” (ie, comprehensive literature search not performed (#4); characteristics of studies not provided (#8); quality of studies was not assessed or considered when conclusions were formulated (#9 and #13)). In general, a high-quality systematic review will score a “yes” on most components presented in the AMSTAR II tool.

Systematic reviews or guidance identified from ‘best sources’ undergo methodological rigor considered to be of high quality and are not scored for quality. ‘Best sources’ include: DURM; DERP; AHRQ; NICE; VA/DoD; CADTH; and BMJ Clinical Evidence.

Ref. *Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008*. doi: 10.1136/bmj.j4008.

AMSTAR II Quality Scoring Template			
1)	**Did the research questions and inclusion criteria for the review include the components of PICO?**		
	For Yes:	ϒ	Yes
	ϒ Population	Optional (recommended)	ϒ No
	ϒ Intervention	ϒ Timeframe for follow-up	
	ϒ Comparator group		
	ϒ Outcome		

2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:
- review question(s)
- search strategy
- inclusion/exclusion criteria
- risk of bias assessment

For Yes: As for partial yes, plus the protocol should be registered and should also have specified:
- meta-analysis/synthesis plan, if appropriate, and
- plan for investigating causes of heterogeneity
- justification for any deviations from the protocol

- Yes
- Partial Yes
- No

3) Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- Explanation for including only RCTs; OR
- OR Explanation for including only non-randomized studies of interventions (NRSI)
- OR Explanation for including both RCTs and NRSI

- Yes
- No

4) Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- searched the reference lists / bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

- Yes
- Partial Yes
- No

5) Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- at least 2 reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR 2 reviewers selected a sample of eligible studies and achieved good agreement (at least 80%), with the remainder selected by one reviewer.

- Yes
- No

6) Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- at least 2 reviewers achieved consensus on which data to extract from included studies
- OR 2 reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80%), with the remainder extracted by one reviewer.

- Yes
- No

7) Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- Justified the exclusion from the review of each potentially relevant study

- Yes
- Partial Yes
- No

8) Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:
- described population in detail
- described intervention in detail (including doses where relevant)
- described comparator in detail (including doses where relevant)
- described study's setting
- timeframe for follow-up

- Yes
- Partial Yes
- No

9)	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in studies that were included in the review?**		
RCTs	**For Partial Yes,** must have assessed RoB from: ϒ unconcealed allocation, and ϒ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	**For Yes,** must also have assessed RoB from: ϒ allocation sequence that was not truly random, and ϒ selection of the reported result from among multiple measurements or analyses of a specified outcome	ϒ Yes ϒ Partial Yes ϒ No ϒ Includes only NRSI
NRSI	**For Partial Yes,** must have assessed RoB: ϒ from confounding, and ϒ from selection bias	**For Yes,** must also have assessed RoB: ϒ methods used to ascertain exposures and outcomes, and ϒ selection of the reported result from among multiple measurements or analyses of a specified outcome	ϒ Yes ϒ Partial Yes ϒ No ϒ Includes only RCTs
10)	**Did the review authors report on the sources of funding for the studies included in the review?**		
	For Yes: Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information, but it was not reported by study authors also qualifies		ϒ Yes ϒ No
11)	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**		
RCTs	**For Yes:** ϒ The authors justified combining the data in a meta-analysis ϒ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ϒ AND investigated the causes of any heterogeneity		ϒ Yes ϒ No ϒ No meta-analysis conducted
NRSI	**For Yes:** ϒ The authors justified combining the data in a meta-analysis ϒ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ϒ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ϒ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review		ϒ Yes ϒ No ϒ No meta-analysis conducted
12)	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**		
	For Yes: ϒ included only low risk of bias RCTs ϒ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.		ϒ Yes ϒ No ϒ No meta-analysis conducted
13)	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**		
	For Yes: ϒ included only low risk of bias RCTs ϒ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results		ϒ Yes ϒ No
14)	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**		
	For Yes: ϒ There was no significant heterogeneity in the results		ϒ Yes ϒ No

	ϒ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	
15)	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** **For Yes:** ϒ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	ϒ Yes ϒ No ϒ No meta-analysis conducted
16)	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** **For Yes:** ϒ The authors reported no competing interests OR ϒ The authors described their funding sources and how they managed potential conflicts of interest	ϒ Yes ϒ No

APPENDIX 2. Methods to Assess Quality of Randomized Controlled Trials.

A bias is a systematic error, or deviation from the truth, in study results. It is not possible to determine the extent biases can affect results of a particular study, but flaws in study design, conduct and analysis of data are known to lead to bias. Biases vary in magnitude but can underestimate or overestimate the true effect of the intervention in clinical trials; therefore, it is important to consider the likely magnitude of bias and direction of effect. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases. Types of common bias are outlined in Table 1.

Table 1. Types of Bias: Cochrane Risk of Bias (modified).

Selection Bias	*Systematic differences* between groups in their *baseline characteristics*. Successful ***randomization*** prevents selection bias because **allocation concealment** is implemented. How participants are allocated to groups must be specified, based on some chance (random) process. Furthermore, steps are taken to ensure group assignments are random by preventing knowledge of forthcoming group allocation.
Performance Bias	*Systematic differences* between groups in the *care provided*, or in exposure to factors other than the primary study intervention. **Blinding study participants and healthcare providers** after group allocation reduces the risk that knowledge of which intervention was received affected the outcomes. Effective blinding ensures all groups receive a similar care experience, including ancillary treatments and diagnostic investigations, and minimizes deviations from the study protocol.
Detection Bias	*Systematic differences* between groups in how study **endpoints are assessed**. **Blinding study investigators** reduces the risk that knowledge of which intervention was received, rather than the intervention itself, affected measurement of study endpoints.
Attrition Bias	*Systematic differences* between groups in *study withdrawals*, either by exclusion or attrition. ***Withdrawals*** from the study lead to incomplete outcome data. ***Exclusions*** refer to situations in which participant data are omitted from analyses despite being available to investigators. ***Attrition*** refers to situations in which outcome data are not available (missed appointments or other protocol deviation, or early study discontinuation).
Reporting Bias	The *selective reporting* of *pre-specified* endpoints based on the results found.

	Reporting bias may arise if results of pre-specified endpoints are omitted or are measured differently or distorted in any way from what was explicitly described in the protocol. Reporting bias may also be introduced when primary endpoints in which statistically significant differences between groups are not found are **selectively reported** while secondary endpoints which found statistically significant differences are over-emphasized.
Other Biases	Other potential sources of bias include investigator's conflicts of interest and study funding sources, which should be collected and presented in the publication. Other biases related to trial designs can be introduced (eg, carry-over from cross-over trials, recruitment bias in cluster-randomized trials, or sources of bias from single-centered trials or particular clinical settings).

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (updated March 2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

Each risk of bias domain is assessed and determined to be LOW, HIGH, or UNCLEAR (**Table 2**). Unclear risk of bias will be interpreted as high risk of bias when quality of evidence is graded (**Appendix x**).

Table 2. Methods to Assess Risk of Bias in Clinical Trials: Cochrane Risk of Bias (modified).

SELECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Inadequate randomization	Sequence generated by: • Computerized random number generator • Random number table	Sequence generated by: • Date of birth • Admission date • Patient identifier number • Alternating numbers	Method of randomization not described in sufficient detail for definitive judgment
Inadequate allocation concealment	Group allocation cannot be predicted because: • Centrally allocated • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Group allocation may be predicted because: • Open allocation • Drug containers may differ in appearance • Envelopes without appropriate safeguards	Method of concealment not described in sufficient detail for definitive judgment
Unbalanced baseline characteristics Note: Statistical tests of baseline characteristics are not helpful.	Important prognostic factors similar between groups at baseline	Important prognostic factors are not balanced, which indicates inadequate allocation concealment or failed randomization.	Important prognostic factors are missing from baseline characteristics (eg, co-morbidities, medical/surg history, concurrent meds)
PERFORMANCE BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Standard of care was not consistent across all groups or sites.	• Study participants could not identify study assignment because blinding was ensured and unlikely to be broken (ie, double-dummy design with matching descriptions) • Protocol standardized across all sites and followed consistently	• Open-label or incomplete blinding • Observed differences in appearance, taste/smell or adverse effects between groups may have broken blinding • Some sites had a different standard of care or varied from protocol which likely influenced effect estimate	Blinding process not described or insufficient information to permit definitive judgment
DETECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**

Investigators who analyzed data un-blinded	• Blinding of data assessors was ensured and unlikely broken • No data blinding or incomplete blinding, but effect estimate unlikely influenced by clearly defined objective endpoints and large magnitude of difference between groups	• No blinding or blinding potentially broken, which likely influenced effect estimates because of inconsistencies between efficacy endpoints or subjective endpoints not well defined.	Blinding process not described or insufficient information to permit definitive judgment
ATTRITION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
High attrition or differential	• No missing data • Reasons for missing outcome data unlikely to influence effect estimates	• High withdrawal rate (eg, >10% for short-term studies; >20% for longer-term studies) • Difference in attrition >10% between groups	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
Missing data handled inappropriately	• Intention-to-treat analysis performed for superiority trials • Intention-to-treat and per-protocol analyses performed and compared for non-inferiority trials • Appropriate censoring rules applied depending on nature of study (eg, last-observation-carried-forward (LOCF) for curative conditions, or for treatments that improve a condition over time like acute pain, infection, etc.) • Reasons for missing outcome data unlikely to influence effect estimates	• As-treated analyses performed with substantial departure from randomized number • Per-protocol analyses or modified-intention-to-treat with substantial amount of missing data • Potentially inappropriate imputation of missing data (eg, LOCF for chronic, deteriorating conditions like HF, COPD, or cancer, etc.)	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
REPORTING BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Selective reporting of endpoints	• Study protocol is available and was followed all pre-specified primary and secondary endpoints are reported • Study protocol is not available, but all endpoints are reported as pre-specified in the study methods	• Not all pre-specified primary and secondary endpoints reported • Primary endpoint(s) reported using measurements, analyses, or subsets of patients that were not pre-specified (eg, post-hoc analysis; protocol change without justification) • Primary endpoint(s) not pre-specified or statistical analyses not described in methods • Inappropriate over-emphasis of positive secondary endpoints in study with negative primary endpoint	Insufficient information to make determination
OTHER BIASES			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of other biases not described in the categories above	• Investigators and authors report no conflicts of interest or study sponsor was not involved in trial	• Conflicts of interest with investigators or authors based on funding source	• Conflicts of interest declarations or funding sources not reported

	design, data analysis or publication • No other potential sources of bias identified	• Study sponsor is involved in trial design, data analysis, and publication of data • Interventions in run-in period may impact effect of interventions post-randomization • Recruitment bias in cluster-randomized trials • Early study termination based on positive results • Carry-over effects in cross-over trials • Protocol deviation based on interim results	• Insufficient information regarding other trial methodology and design to make a determination

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (updated March 2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability (directness) of the evidence to Oregon's populations (**Table 3**).

Table 3. PICOS Domains that Determine Applicability

PICOS Domain	Conditions that Limit Applicability
Patients	• Narrow eligibility criteria and broad exclusion criteria • Significant differences between the demographic characteristics of the study population and the Oregon's populations of interest • Narrow or unrepresentative severities in stage of illness or comorbidities (eg, only mild or moderate severity of illness included) • Run-in period with high exclusion rate for non-adherence or adverse effects • Event rates in study much lower/higher than observed in Oregon's populations of interest
Interventions	• Dose, frequency of administration, formulation not reflective of clinical practice • Intensity/delivery of interventions not feasible for routine use in clinical practice • Concomitant interventions likely over- or underestimate effectiveness of therapy
Comparators	• Inadequate dose or frequency of administration of comparator • Use of inferior or substandard comparator relative to other alternatives
Outcomes	• Short-term or surrogate endpoints assessed • Instrument used to assess endpoints is difficult to use or impractical to implement in clinical practice • Composite endpoint used that mix outcomes of different significance
Settings	• Standards of care in study setting differ markedly from clinical practice • Monitoring/visit frequency not feasible for routine use in clinical practice • Level of care provided from specialists does not reflect clinical practice where intervention is likely to be used

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (updated March 2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

APPENDIX 3. Methods to Assess Quality of Clinical Practice Guidelines.

Clinical practice guidelines are systematically developed statements that assist clinicians in making clinical decisions. However, guidelines can vary widely in quality and utility. The Appraisal of Guidelines, Research, and Evaluation (AGREE) Instrument (www.agreetrust.org) assesses the methodologic rigor in which a guideline is developed and used. The consolidated AGREE II Global Rating Scale (GRS) is an easy-to-administer, validated instrument that consists of 4 items (Table x). Each item is rated on a 7-point scale, from 0=lowest quality to 7=highest quality. In general, a high-quality clinical practice guideline will score 5-7 points on each component of the AGREE II-GRS.

Table x. AGREE II Global Rating Scale (modified)**.**

	ITEM	DESCRIPTION
PROCESS DEVELOPMENT		
1	Rate the guideline development methods. **SCORE:**	• Appropriate stakeholders were involved in the development of the guideline. • The evidence-base was developed systematically. • Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs were made.
PRESENTATION STYLE		
2	Rate the guideline presentation. **SCORE:**	• The guideline was well organized. • The recommendations were easy to find.
CLINICAL VALIDITY		
3	Rate the guideline recommendations. **SCORE:**	• The recommendations are clinically sound. • The recommendations are appropriate for the intended patients.
COMPLETENESS OF REPORTING		
4	Rate the completeness of reporting, editorial independence. **SCORE:**	• The information is complete to inform decision-making. • The guideline development process is transparent and reproducible.
5	The views of the funding body did not influence the content of the guideline. **SCORE:**	• The name of the funding body or source of funding is explicitly stated (or explicit statement of no funding) • There is a statement that the funding bodies did not influence the content of the guideline, or at least *how* the guideline development group addressed *potential* influence from the funding bodies.
6	Competing interests of guideline development group members were recorded and addressed. **SCORE:**	• A description of the types of competing interests is considered. • Methods by which potential competing interests were sought. • Competing interests are described. • How the competing interests influenced the guideline process and development of recommendations is described.