Arivale®

Clinical Recommendation White Paper

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Introduction

Arivale uses a systems approach to help improve overall health and wellbeing of its members. Arivale integrates and analyzes individuals' genetics, clinical labs, and behavioral assessments to create personalized plans that are delivered by licensed healthcare professionals.

Dietary, lifestyle, and/or supplements may aid an individual on their path for wellness. For some of these interventions, there exist public health guidelines or opinions from expert working groups or professional societies, of which we adopt and implement. However, for other interventions such guidelines and opinions are lacking. To address this, at Arivale we have created a formal research process and evidence-based rating system to maintain consistency, accountability, and documentation of the interventions we recommend. In order to be transparent with our approach, this white paper describes the methods used to determine the interventions we recommend.

Research Process

An intervention (without a public health guideline or expert professional group opinion) may be selected for a full research review for a variety of reasons. Common reasons include Arivale Coaches or Members requesting information (e.g. "Are curcumin supplements helpful for age-related cognitive decline?"), the Clinical Team needing evidence-base for a new or changing recommendation (e.g. "Do B-vitamin supplements increase cancer risk?"), or a focus in the popular media that is creating questions in relation to current Arivale recommendations (e.g. "Is a ketogenic diet effective for weight loss?"). Below is the process we employ to evaluate the scientific evidence for an association between a single intervention and a specific desired health outcome.

- To ensure the most comprehensive literature search, we start our research process by defining the scientific question of interest, typically in the form of: 'What is the effect of [intervention] on [health outcome] in [population]'.

- Once the scientific question is well-defined, we create an exhaustive list of all of the "keywords" or word permutations that have been used to refer to the intervention, health outcome, and the population of interest.

- A PubMed search is then conducted. The list of keywords is used, in conjunction with Boolean operators and other special characters. This comprehensive literature search will be further expanded by running new PubMed queries with any additional relevant keywords that may be identified during the curation.

- If the PubMed search comes up with >50 publications, we restrict the search to systematic reviews and meta-analyses (unless there are none). If >50 publications, we still include individual studies that are more recent than the most recent systematic review.

- Lastly, we select the publications that are relevant for the scientific question of interest and retrieve the full text articles. Publications without an available full text will not be included in the rating process. If a single study is part of a meta-analysis, we include only the meta-analysis in order to ensure that no individual study will be considered twice. We do not include non-systematic reviews (except for Cochrane reviews), case studies, or anecdotal reports from clinical practice for assessing the level of evidence.

- Each literature search is fully documented, including the total number of search results, the number of relevant results, the date the search was run, the exact search terms and logic used for the query, and if any filters (e.g. publication dates, article type) were used for the search results.

Quality Rating of a Publication

For each relevant publication from the literature search above, we assess whether it meets specific quality criteria. Below are the quality criteria for each type of publication:

TYPE OF PUBLICATION	QUALITY CRITERIA
Meta-analyses and systematic reviews	1. Research question is clearly stated. 2. Words for electronic search listed. 3. Inclusion/exclusion criteria for studies included. 4. No significant heterogeneity amongst studies. Substantial differences in the study design or patient populations signify heterogeneity and suggest that the data from the studies should not have been combined. 5. Results are displayed in a plot (forest/funnel plot). 6. Sensitivity analysis included. 7. Funding sources stated & no conflicts of interest.
Randomized clinical trials (RCTs)	1. Research question is clearly stated. 2. A single primary endpoint was defined prior to trial (should not be multiple endpoints). 3. The randomization worked (i.e. key characteristics of treatment groups are alike). 4. Study was double blinded and used placebos (N/A for interventions implemented physically, e.g. meditation). 5. Funding sources stated & no conflicts of interest.

Population/epidemiology studies: *Case-Control* *Cohort* *Cross-sectional*	1. Research question clearly stated. 2. Study population clearly defined. 3. Subjects selected or recruited from the same or similar populations/time period (if not then accounted for in statistical analysis). 4. Inclusion and exclusion criteria pre-specified and applied uniformly to all participants. 5. Intervention/factors of interest measured prior to the outcome(s) being measured. 6. Sufficient time to examine possible effect of intervention/factors on outcome(s). 7. Intervention/factors of interest assessed more than once. 8. Statistical adjustment for key potential confounding variables (things that could impact the relationship between the exposure and outcome). 9. Funding sources stated & no conflicts of interest.

After assessing quality criteria, each study is rated as either good, moderate, or poor quality. The following are the definitions for the ratings:

- Good quality: Includes all of the criteria for the given publication type. Cochrane reviews (a type of systematic review) are automatically considered "good quality".
- Moderate quality: Meets 3 or more of the criteria for the given publication type.
- Poor quality: Meets fewer than 3 criteria for the given publication type.

Body of Scientific Evidence

Once the quality of each relevant study is assessed, we evaluate the overall body of evidence for a given intervention and health outcome by tallying the number of publications with a:

- Statistically significant positive (beneficial) association.
- Statistically significant negative (harmful) association.
- Null association (no statistically significant association found).

Based on the counts of the various types of associations and quality of the relevant publications we assign a confidence rating for the intervention and desired health outcome in question. For this purpose, we have established a five-level confidence rating system:

- **Confidence Level 1:** Lack of significance
- **Confidence Level 2:** Unknown significance
- **Confidence Level 3:** Moderate significance
- **Confidence Level 4:** Strong significance
- **Confidence Level 5:** Very strong significance

We have defined different case scenarios that can lead to a given confidence level, for example:

- A lack of significance (Confidence Level 1) may be due to no association between the intervention and the outcome when assessing good and moderate quality studies. In addition, a lack of significance may be due to conflicting results, where there are just as many publications with and without a significant association.

- A strong significance (Confidence Level 4) could be due to no conflicted data and at least 4 publications, with a minimum of one good quality study. A strong significance could also be due to the scenario where there is some conflicted data but there are a greater number (2 or 3 times) of publications reporting a significant association than not.

Overall, the different case scenarios reflect the degree of controversy for the findings, as well as the number and quality of the relevant publications that were included from the research process.

Efficacy, Safety, and Recommendation Procedure

Lastly, before this intervention can be recommended, we must assess its efficacy and safety. The Confidence Level system above, does not explicitly state a threshold by which an Arivale coach can recommend the intervention. The Confidence Level system does not comment on the safety of the intervention. To do this, we assign these interventions into the following categories: ***1. Safe and Effective, 2. Unknown Benefit, 3. Demonstrated Lack of Efficacy and 4. Safety Concern***.

- **Safe and Effective:** An Arivale Coach can recommend this type of intervention. These interventions have been assigned an Arivale Confidence Level of a 3 or above (moderate to very strong significance). Furthermore, the majority of publications for this intervention have beneficial associations and there are no known safety issues or major adverse effects.

- **Unknown Benefit:** An Arivale Coaches will remain "neutral" around this intervention meaning they will not proactively recommend this intervention, and if asked by a member will state that there is not enough evidence to support recommending the intervention. But a member can implement the intervention (e.g. take a supplement) at their own discretion. These interventions have been assigned an Arivale Confidence Level of 1 or 2. There are three scenarios of Unknown Benefit:
  - Safe, Lack of Data: Studies do not yet exist to evaluate the effectiveness of the recommendation. There are no known safety issues.
  - Safe, Conflicting Data: There is conflicting data that prevents a clear determination about whether the intervention is effective. There are no known safety issues.
  - Research Pending: Arivale has not yet researched the intervention.

- **Demonstrated Lack of Efficacy:** An Arivale Coach will not recommend this type of intervention. These interventions have been assigned an Arivale Confidence Level of 1 or 2. These interventions lack efficacy, meaning the majority of publications have found null associations.

- **Safety Concern:** An Arivale Coach will not recommend this type of intervention. Regardless of the Confidence Level assigned, the intervention has some safety concerns or adverse effects.

**** Note:*** *Arivale does not diagnose or treat disease. A Member's physician may choose to employ interventions despite the lack of evidence-based support and/or safety. Arivale's default position is to support the recommendations and medical judgment of the Member's physician/ healthcare team.*

Conclusion

Currently, there is no standard in the wellness industry for researching, evaluating, and recommending interventions. At Arivale, we are determined to be transparent and rigorous in this process. We advocate for a better standardization so that consumers can have an unbiased evidence-based review of the strengths and limitations of diet, lifestyle, and supplement-based interventions. Ultimately, we hope that this will empower consumers on their path towards wellness.