1.a. **Full Title:** Accounting for practice effects in serial cognitive function assessments for longitudinal cohort studies.

b. **Abbreviated Title (Length 26 characters):**

2. **Writing Group:**
   Rajesh Talluri, B. Gwen Windham, Alden Gross, James Russell Pike, Tom Mosley, Michael Griswold, Melinda Power, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __RT__ [please confirm with your initials electronically or in writing]

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3. **Timeline:** Planned manuscript preparation and submission 6 months

4. **Rationale:**

In dementia research, cognitive function and cognitive decline measures are necessary to define dementia and are widely used to understand factors affecting dementia and to evaluate novel treatments to improve cognitive function. It is therefore of paramount importance that cognitive measures reflect an individual’s true cognitive ability. In longitudinal studies, cognitive function is evaluated using standardized tests, typically with the same versions administered over time. As participants are exposed to the same cognitive test repeatedly, an individual may learn and adjust to the test. This effect, called the practice/learning/retest effect, may confound the true cognition effect of the individual. It is very difficult to delineate the practice effect from true cognitive ability because the practice effect is also an integral part of cognitive ability of the individual. Alternatively, the ability to demonstrate a practice or learning effect could signal preserved cognitive functioning and thus help distinguish among people with similar cognitive scores. Practice effects can depend on different factors such as familiarity with the test, familiarity with the testing environment, recall effects, procedural learning, test complexity and the individual person’s cognitive characteristics.
Practice effects are reportedly pervasive and often underappreciated. Ignoring practice effects may lead to underestimation of cognitive decline and overestimation of baseline cognition function of an individual which may bias the results of the study. In longitudinal cohort studies where the effect of an exposure on cognitive impairment is being evaluated, ignoring practice effects could lead to the overestimation of the effects in absence of specialized control groups. Practice effects have been observed with repeated testing in individuals with Alzheimer’s disease. Generally, practice effects are thought to influence tests repeated over short time intervals, however, practice effects have been shown to persist over long time periods even with time intervals up to 4 years.

Several approaches have been proposed to reduce practice and retest effects such as practicing before the test or the use of alternative forms. Yet, even if these approaches are utilized additional statistical corrections are often necessary. Several statistical modeling approaches have been proposed to account for practice effects using reliable change indices, linear mixed models and other data analysis approaches. These approaches have several limitations due to confounding of practice effects with other covariates such as age.

Despite a plethora of research underscoring the importance of practice effects in longitudinal cognition studies, no general consensus on how to account for the impact of practice effects on cognition measures exists. In this manuscript, we propose to develop a statistical framework to model the effect of practice/learning effects on a longitudinal cohort for the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study. We hypothesize that this would lead to better characterization of the true cognition function in individuals and better estimation (lower bias/variance) of effect of other risk factors on cognitive function and cognitive decline. Better understanding of true cognitive functioning would lead to better prediction of future cognitive decline in individuals. This would have profound implications for public health because early detection of dementia (due to better predictive models due to statistical efficiency) would greatly improve prognosis and significantly improve quality of life for aging individuals.

5. Main Hypothesis/Study Questions:

Hypothesis – We assume that the true cognitive measurement is interwoven with the practice effect and that this effect may be reinforced every time the test is administered. We also assume that these practice effects decline with additional visits and over long periods of time. We propose to model the practice effects using the above two assumptions using an exponential decay model for the practice effects. We hypothesize that this will lead to more accurate (less variance) estimation of the practice effects which would reduce the uncertainty in the measured cognition.

Secondary Hypothesis: If a novel test was introduced later in the study, will there be any transfer of practice effects on this test from the other tests that the individual has practiced? We hypothesize that this will be dependent on the type of the test.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Design:
Longitudinal analysis of all participants in completed ARIC study.

Inclusion criteria:
Participants in ARIC with more than one cognitive measurement.

**Exclusions:**
Individuals without cognitive measurement data

**Outcomes:**
Primary outcome: Cognitive function using z-scores of Digit substitution test, Delayed word recall test and Word fluency test.

**Exposures:**
Cognitive function will be evaluated as a continuous and standardized variable.

**Covariates:**
We will consider the following covariates: APOE genotype, age, BMI, sex, race-site, educational level, smoking, alcohol use, diabetes, systolic blood pressure, diastolic blood pressure, antihypertensive medications, total cholesterol and HDL cholesterol.

**Analysis:**
This manuscript will develop novel statistical methods to account for learning/practice effects in serial cognitive assessment for the ARIC study. The following data generation process is used to model the practice effects.

**The Data generation process**

We assume that the true cognition \( Y \) is influenced by many factors \( X = [X_1, \ldots, X_n] \) and that it can be modeled as

\[
Y = f(X)
\]

where \( f \) could be any nonlinear function.
Initial measurement model

The first time an individual is given the cognition test there is no learning effect because the individual was not exposed to the test before. The measurement model for an individual i could be written as $Y_i = f(X_i) + \epsilon_i$. Assuming there are N individuals in the study this can be vectorized as

$$Y = f(X) + \epsilon$$

where $Y$ is a $N \times 1$ vector containing measurements of all N individuals, $X$ is the $N \times p$ design matrix containing the covariates and $\epsilon$ is the $N \times 1$ error vector.

Secondary measurement model

The second time the individual takes the cognition test he is already familiar with the test hence he has a learning effect on his cognition measurement. We include this effect in the model as:

$$Y_{t_2} = f(X_{t_2}) + g(X_{t_2}, t_2 - t_1) + \epsilon$$

where $g(X_{t_2}, t_2 - t_1)$ is the learning effect. The learning effect decays over time and we need to consider this time interval when modeling the learning effects.

Post-secondary measurement model

From the third time onward there will be another reinforced effect from each of the previous tests taken. We model this at the kth visit as follows.

$$Y_{t_k} = f(X_{t_k}) + g_1(X_{t_1}, t_k - t_1) + g_2(X_{t_2}, t_k - t_1) + \cdots + g(X_{t_{k-1}}, t_k - t_{k-1}) + \epsilon$$

where $t_1, \ldots, t_k$ are the times of the tests.

For simplicity we could assume the learning effect as an exponentially decaying function with time, which is a reasonable assumption.

Modeling practice effects using exponential decay

The data generation process is as follows:

1. At the first test at time $t_1$

$$Y_{t_1} = \hat{Y}_{t_1} + L_0 + \epsilon$$

2. where $\hat{Y}$ is the predicted cognition $L_0 = 0$ (or $K_0$ may be negative) is the Learning Effect due to no test familiarity.

3. At test 2

$$Y_{t_2} = \hat{Y}_{t_2} + L_1(t_2 - t_1) + \epsilon$$

4. $L_1$ is the Learning Effect due to test 1 performed at time $t_1$. As we know that the practice effect decays over time, we can model the practice effect as:

$$L_1(t_2 - t_1) = K_1 e^{-\alpha(t_2 - t_1)}$$

5. We can see that if $t_1$ is close to $t_0$, there will be a big learning effect, however if $t_1 >> t_0$ there will be little or no practice effect.
\[ Y_{t_2} = \overline{Y}_{t_2} + K_1 e^{-\alpha(t_2-t_1)} + \epsilon \]

6. At test 3 there will be 2 learning effects, one from test 1 and another from test 2

\[ Y_{t_3} = \overline{Y}_{t_3} + L_1 (t_3 - t_1) + L_2 (t_3 - t_2) + \epsilon \]

\[ Y_{t_3} = \overline{Y}_{t_3} + K_1 e^{-\alpha(t_2-t_1)} + K_2 e^{-\alpha(t_3-t_2)} + \epsilon \]

at the ith test

\[ Y_{t_i} = \overline{Y}_{t_i} + K_1 e^{-\alpha(t_i-t_1)} + K_2 e^{-\alpha(t_i-t_2)} + \ldots + K_{i-1} e^{-\alpha(t_i-t_{i-1})} + \epsilon \]

\[ Y_{t_i} = \overline{Y}_{t_i} + \sum_{j=1}^{i-1} K_j e^{-\alpha(t_i-t_j)} + \epsilon \]

**Base learning Effect**

- We assume that \( \alpha \) is constant for all learning effects (The meaning of this assumption is that we assume learning effects at each test to decay at the same rate).

- We do not assume that \( K_i \) are constant. This is because the amount you learn may vary with each test. Intuitively, the first time you take a test you may score lower, the second time you take a test you are familiar and the third time you may be accustomed. However,
the fourth time there may not be as much to learn. Consequently, we expect to model \( K_i \) based on “expert knowledge” as in the figure.

- \( K_i \) will also vary from individual to individual depending on the covariates. Then an example formulation of the model for \( K_i \) would be:
  
  \[
  K_i = \gamma_0 + \gamma_1 \text{age} + \gamma_2 \text{bmi} + \gamma_3 \text{sbp} + \gamma_4 \text{dbp}
  \]
  
  where \( \gamma_0 \) is the average learning effect for the \( i \)th test when the covariates are standardized.

- \( \gamma_i \) is estimated without biases from a reference population. In this scenario it is from assuming \( K_0 = 0 \) at the first test and developing a comprehensive prediction model for cognition using the first test data.

**Modeling \( \gamma_i \)**

We need a model for \( Y \) which should be able to predict the cognition measure with reasonable accuracy. We propose a model with all covariates and their interactions with age as the model that closely mimics a linear mixed model. As all longitudinal data possibly have interactions with time, the corresponding step is to treat age as time in the reference model to estimate \( \gamma_i \).

An example of the reference model is:

\[
Y = \beta_0 + \beta_1 \text{age} + \beta_2 \text{bmi} + \beta_3 \text{sbp} + \beta_4 \text{dbp}
+ \beta_{21} \text{bmi} \times \text{age} + \beta_{31} \text{sbp} \times \text{age} + \beta_{41} \text{dbp} \times \text{age}
\]

This model will be implemented using a Bayesian hierarchical model using vague priors over the model parameters. We will use simulations inspired by ARIC V2, V3, V4, V5 datasets to validate the proposed model. The effects of learning effects in 2 scenarios

1. Longitudinal studies with cognitive decline as outcome and
2. Cross sectional association studies with dementia as outcome.

The proposed model will be used to analyze ARIC V2, V3, V4, V5 data, to examine factors affecting cognition score. The results when accounting for learning effects (proposed method) versus the results when not accounting for learning effects, will be provided to assess the practical impact of learning effects. We will also compare with existing methods for correction of practice effects such as reliable change indices\(^{12}\), mean difference correction\(^{16}\) and model based correction\(^{17,18}\). We will also use the above statistical model to estimate the magnitude of learning effects in tests that were included in the middle of the study to understand if any learning is transferred from the other tests.

7.a. Will the data be used for non-CVD analysis in this manuscript? X __ Yes    __ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? __x_ Yes    ____ No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)
8. a. Will the DNA data be used in this manuscript? ____ Yes    __X__ No 

8. b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? __X__ Yes    ____ No 

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.csc.unc.edu/ARIC/search.php  

__X__ Yes    _______ No 

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?  

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ X ___ Yes   ____ No 

11. b. If yes, is the proposal  
____  A. primarily the result of an ancillary study (list number*_____)
__X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.06; 1999.01; 2004.01 )

*ancillary studies are listed by number at http://www.csc.unc.edu/aric/forms/ 

12. a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire. 

12. b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.csc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central. 

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _____ No.
References