Methods: Mind the Gap

Webinar Series

Choosing Sample Sizes for Multilevel and Longitudinal Studies Analyzed with Linear Mixed Models

Presented by:

Keith E. Muller, Ph.D.

Deborah H. Glueck, Ph.D.

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Choosing Sample Sizes for Multilevel and Longitudinal Studies Analyzed with Linear Mixed Models

Keith E. Muller
Department of Health Outcomes and Biomedical Informatics
University of Florida College of Medicine
and
Deborah H. Glueck
Department of Pediatrics
University of Colorado School of Medicine

Conflicts of Interest

The authors declare no conflicts of interest.

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Other Team Members

- The version of the software that will be discussed was primarily developed by Alasdair Macleod, Elizabeth Litkowski, Qian Li, and Dr. Jiang Bian. Many others created previous versions (most notably Dr. Sarah Kreidler).
- The educational technology that will be discussed was primarily developed by Dr. Albert Ritzhaupt, Dr. Max Sommer, Dr. Natercia Lourinho Moura do Valle, and Michelle Zamperlini. Many others helped create the original course content (most notably Jessica R. Shaw).

Outline

- An original study is *reproducible* if a new sample of data collected under the original protocol is likely to lead to the same conclusions as the original study.
- To be reproducible, a study must have good statistical power.
- Advances in power theory make it accurate and fast to compute power for linear mixed models.
- Free point-and-click software makes it easy to compute power.
- Planning a longitudinal clinical trial illustrates the process.
- No power software covers everything. There is much room for future methodological research, and extensions to the software.

Ethics of Sample Size

- Scientific knowledge is public and reproducible.
- If the sample size is too small, a study may be inconclusive and waste resources.
- If the sample size is too large, then a study may expose too many participants to possible harm.
- Ethical designs have sample size that is large enough and not too large.

Choosing the Correct Sample Size Requires Alignment

- Conscientious study planners routinely align
  data analysis with study design and
  study design with scientific goals.
- Aligning power analysis with data analysis is not routine because it requires:
  statistical theory,
  accurate computational forms, and
  easy to use software.
- Until recently, linear mixed models lacked all three.

Power Theory for Many Linear Mixed Model Hypotheses

- The core statistical theory of power analysis for a broad swath of general linear mixed models used in health research is in Muller et al. (1992) and Chi et al. (2019).
- With no missing data, the mixed models of interest give a Wald statistic that is equivalent to the Hotelling-Lawley trace.
- With no missing data, the power results are exact in many important cases.
- References in the bibliography give a path to the underlying theory and the equally important computational methods.

Why not Run Simulations?

- Computer simulations take longer because they take time to:
  write and debug the simulation,
  validate the simulation,
  iteratively change the design, and
  generate enough points for a power curve.

- Single programmers with a deadline are vulnerable to:
  mistakes in initial assumptions,
  mistakes in coding,
  mistakes in modules written by others and
  an inability to validate with independent target values.

We Give You Easy-to-Use and Validated Power Software

- We have built a point-and-click application for web browsers.
- The wizard-style software is free, and copyleft under the GNU public license so that it will always be free.
- A sequence of dialog boxes leads a user through well-defined steps.
- The software is validated to industry standards.
- Software development was funded by five NIH grants to our group.

Features of GLIMMPSE Software

- Free access is available to anyone.
- A user only needs a web browser.
- No programming expertise is needed.
- No mathematical notation is used.
- A partial or complete study design can be saved for later use.
- The software works on computers, tablets and smartphones.
- The computations are done on a remote server.

GLIMMPSE Gives Power and Sample Size for Many Designs

- Single level designs
  - Cluster- or group-randomized trials, like the TAAG study.
  - Observational studies with clustering, like the ECHO consortium of cohorts.
- Randomized block (randomized complete block) designs, like the CAPS gardens trial.
- Multilevel observational or randomized designs like the ENRICH randomized controlled trial, with participant within nurse and nurse within clinic.
- Multivariate designs, like a study of cord blood chemokines in children in the Healthy Start cohort.
- Studies with both clustering or grouping and repeated measures, like a study of micronutrients throughout pregnancy for women who are cohort members in the ECHO consortium.

Our Track Record

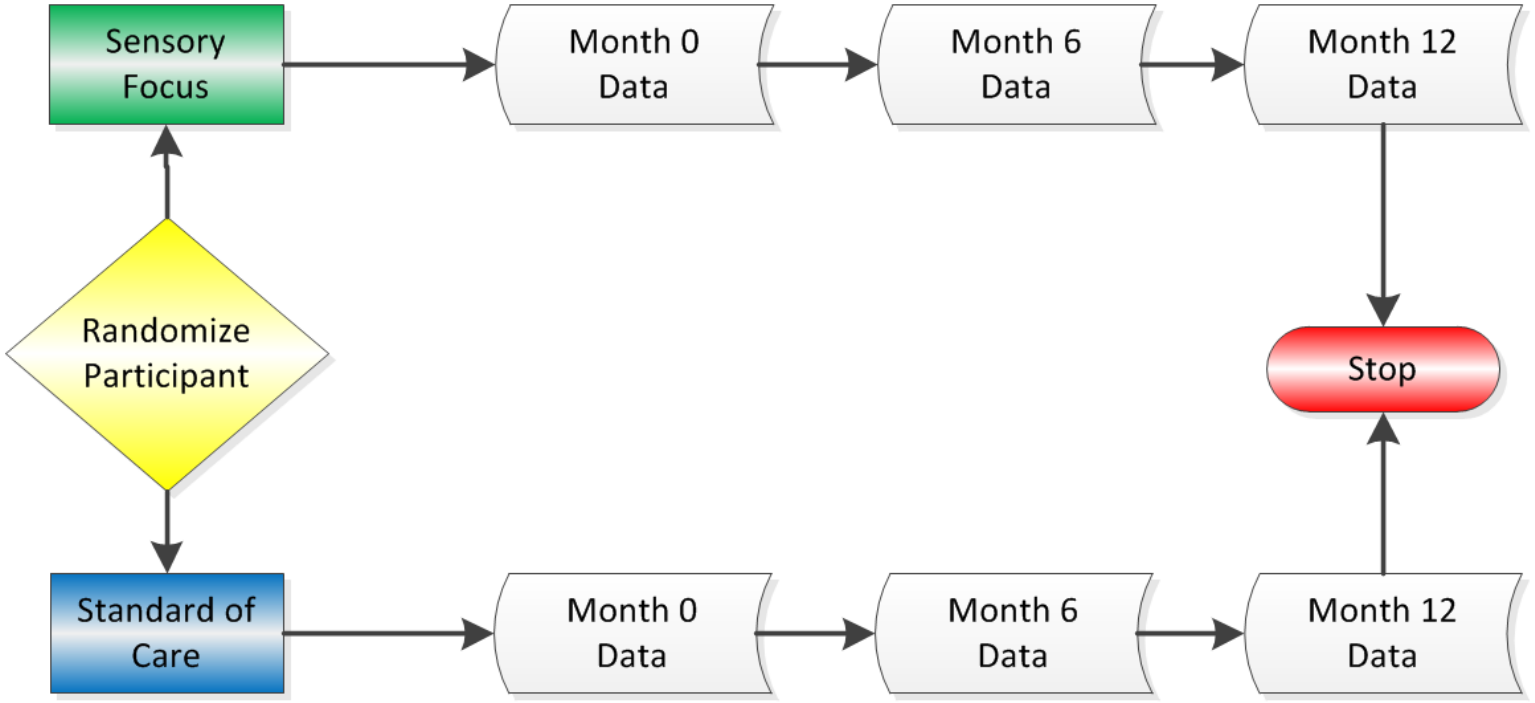
- Users cited our software in 288 peer-reviewed articles since 2013, with exponential growth.
- Our software was cited in manuscripts which also cited over $100,000,000 in NIH grants.
- Users citing our software are funded by 12 NIH Institutes and Centers.
- Manuscripts citing our software encompass all 16 Medical Subject Headings.
- In the last year, Google Analytics counted more than 10,000 website visits.
- In the last year, some 2,700 power and sample size analyses were completed with GLIMMPSE.
- Over a sampling of 82 days, 819 users created logins, with 138 (17%) from US universities.
- Only 20% of users (N =169) had foreign country codes.

An Example Power Analysis: Proposed Randomized Trial

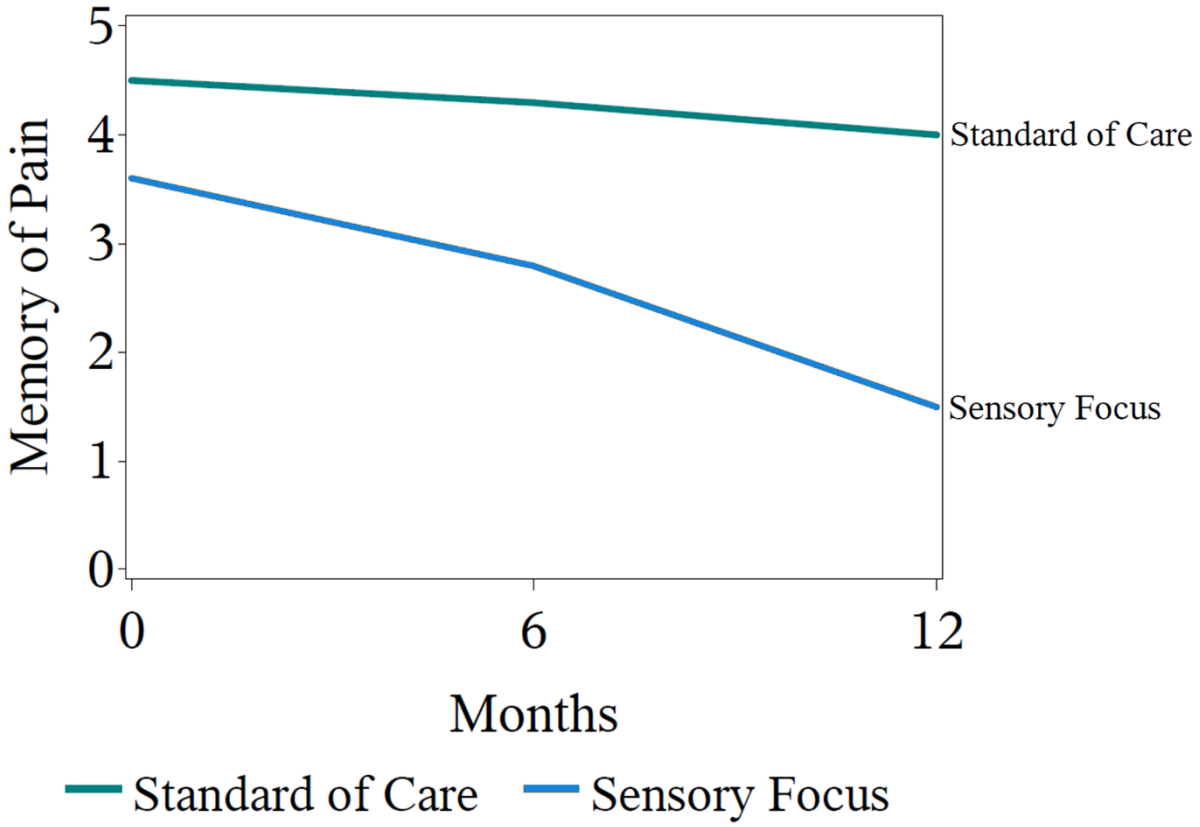
- The primary trial outcome will be the memory of pain reported after a root canal.
- The memory of pain will be recorded immediately, at 6 months and 12 months, so each participant will have 3 repeated measures.
- Participants will be included if they have a coping style with low perceived control and high desired control.
- Participants will be randomized to one of two treatment arms: sensory focus or standard of care.

(Proposed study based on Logan et al., 1995)

Proposed Randomized Trial



Hypothesized Memory of Pain Pattern



Study Population for Proposed Randomized Trial

- Participants will be included if they have a coping style with low perceived control and high desired control.
- Results from the previous study predict 30 patients / week.
- The previous study had a 40% consent rate.

Inputs for Power Analysis

- Type I error rate:
- Desired power:
- Loss to follow-up:

Inputs for Power Analysis

- Type I error rate: 0.05
- Desired power:
- Loss to follow-up:

Inputs for Power Analysis

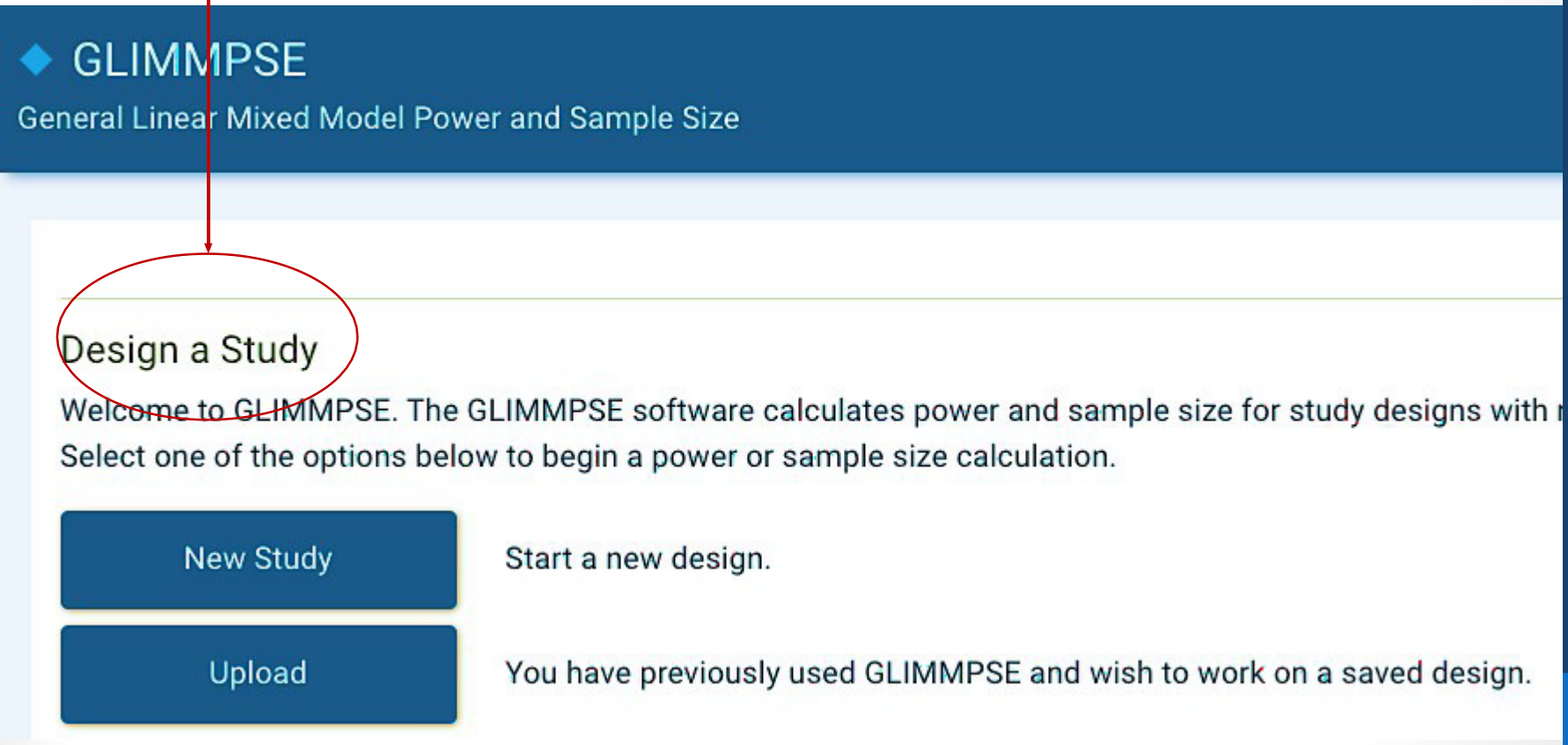
- Type I error rate: 0.01
- Desired power: 0.85, 0.90, 0.95
- Loss to follow-up:

Inputs for Power Analysis

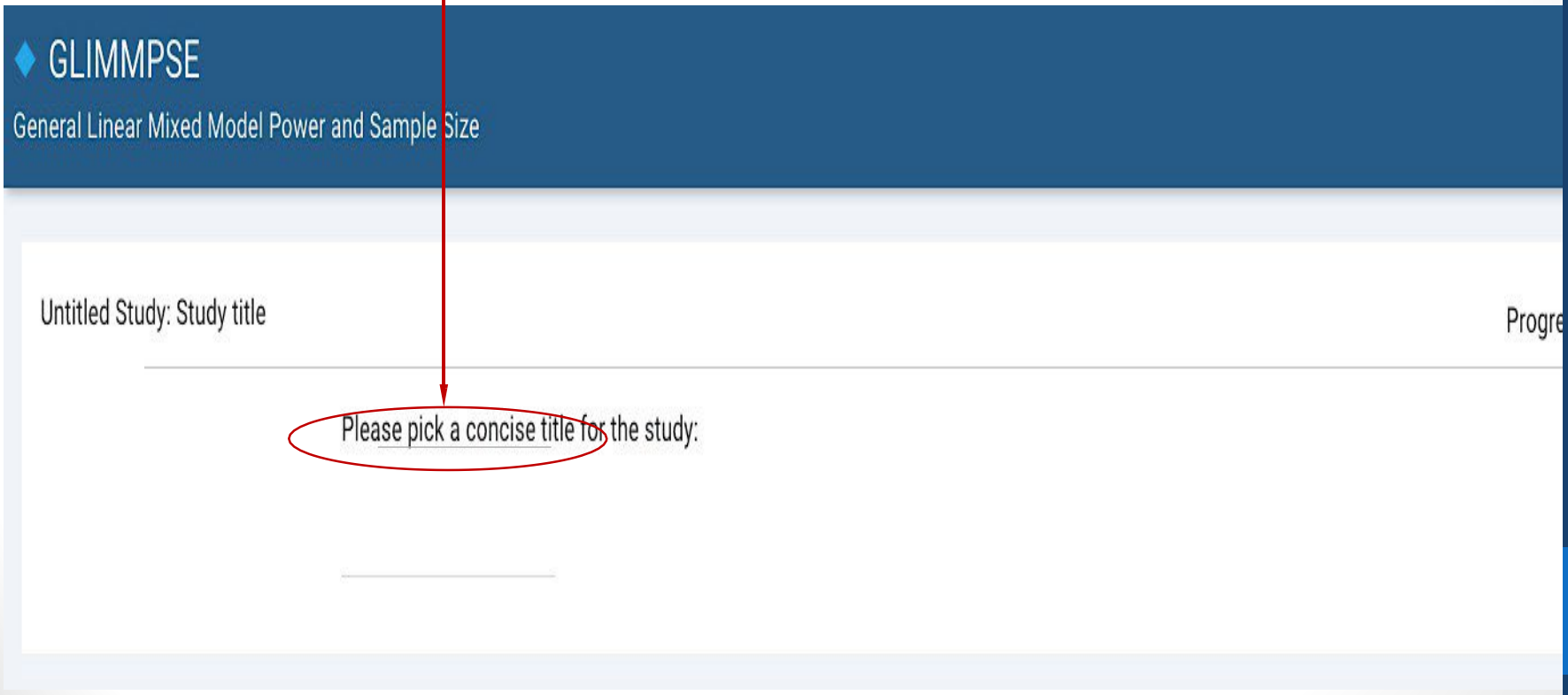
- Type I error rate: 0.01
- Desired power: 0.85, 0.90, 0.95
- Loss to follow-up: 25%

Create a Study Design

- Click the "New Study" button to start a new power and sample size analysis, or
- Click the "Upload" button to upload a json file with a previous study design that you have saved.

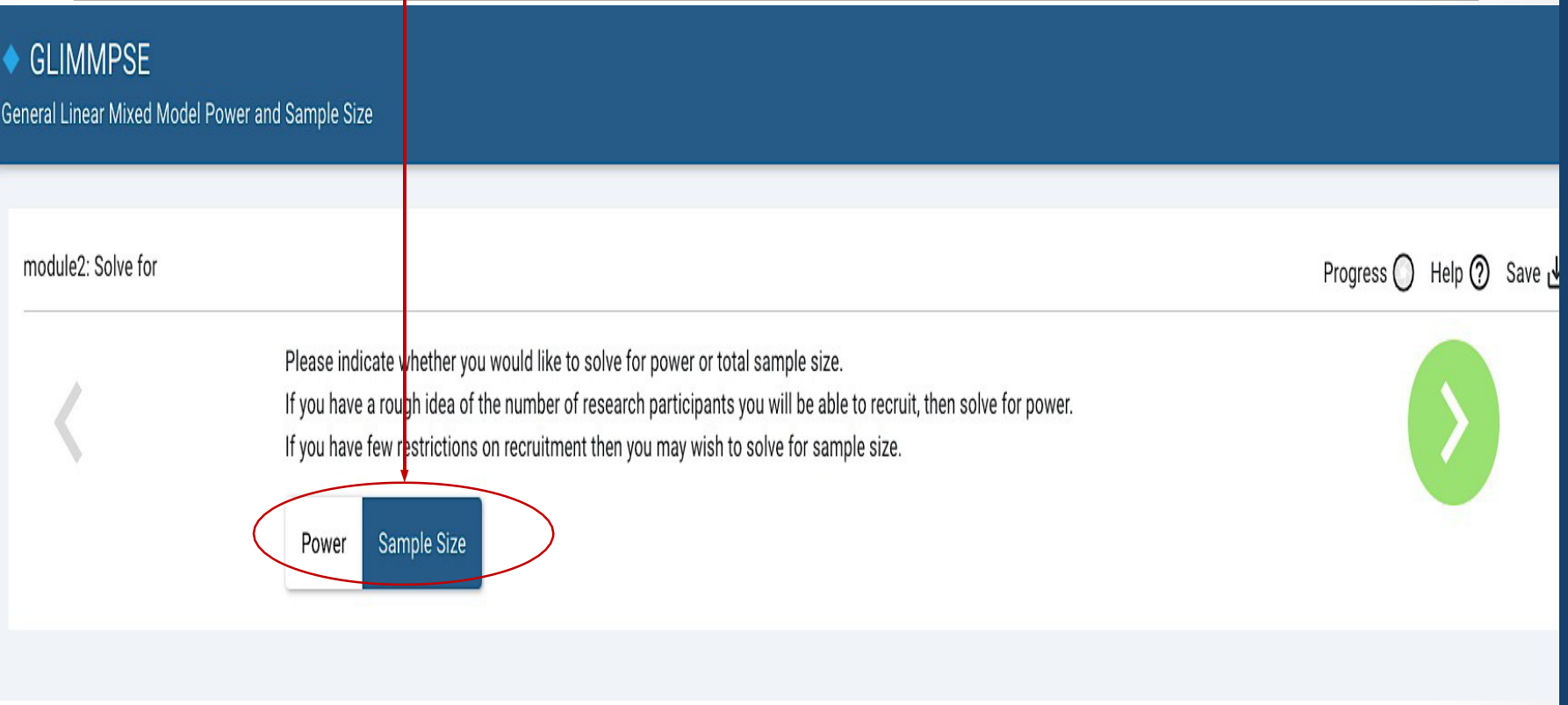


For a new study: Add title here.



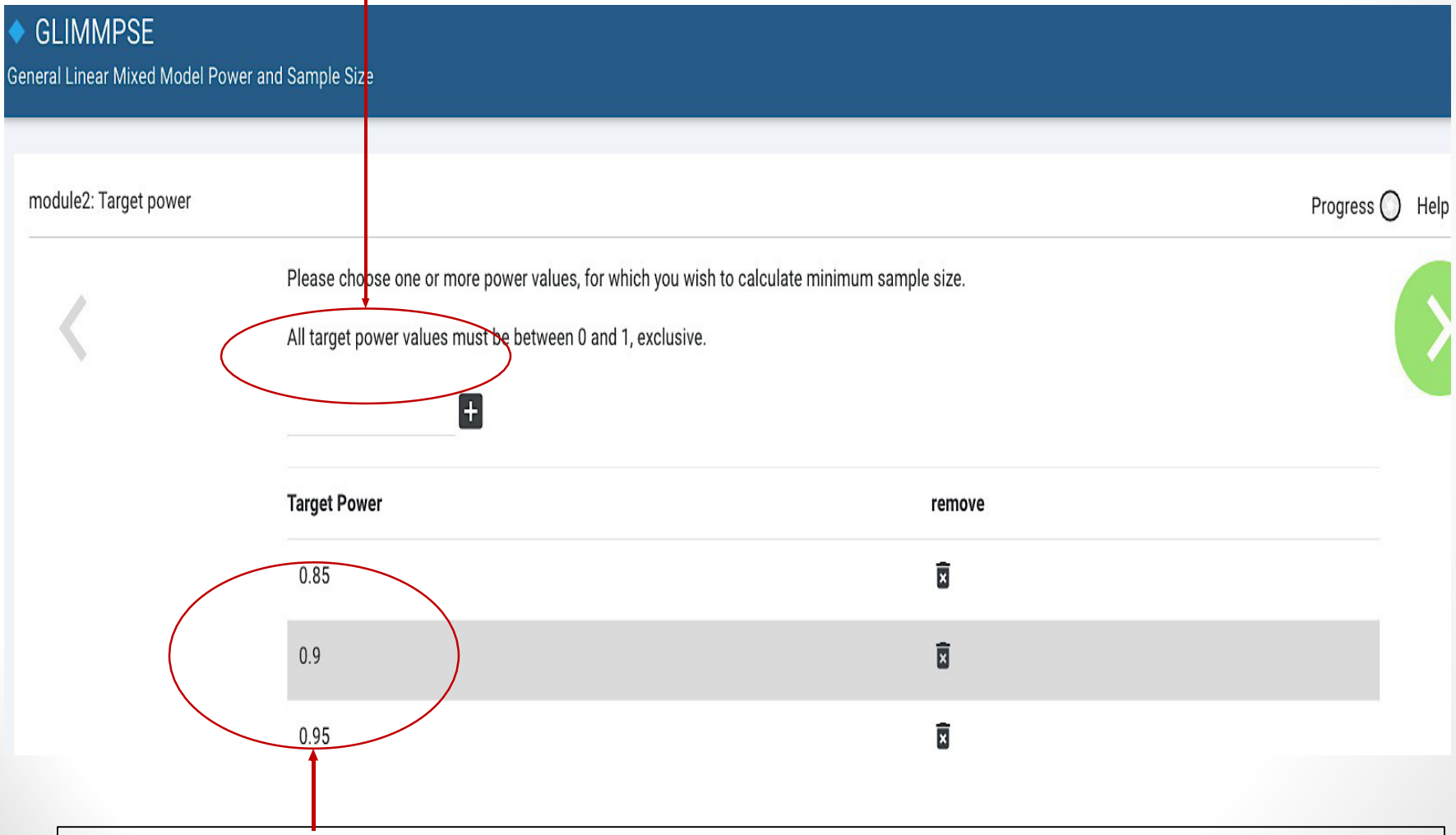
Solving for

Click the "Power" or "Sample Size" button.
In this case, we are solving for sample size.



Desired Power

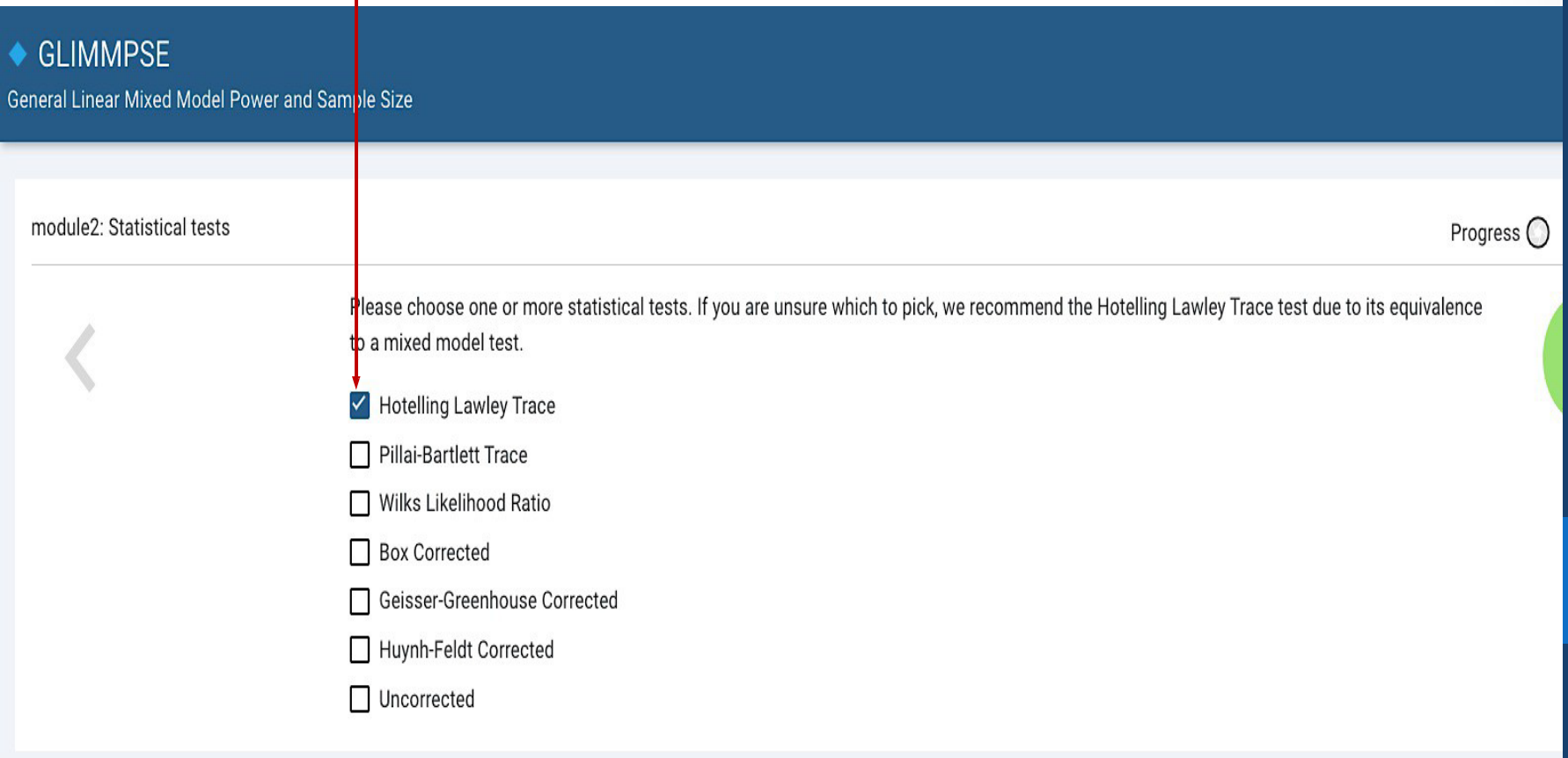
On the "Target Power" screen, we indicate that we want power values of 0.85, 0.90 and 0.95. Type each desired power value and hit enter after each.



You can specify multiple values of interest for the same GLIMMPSE design.

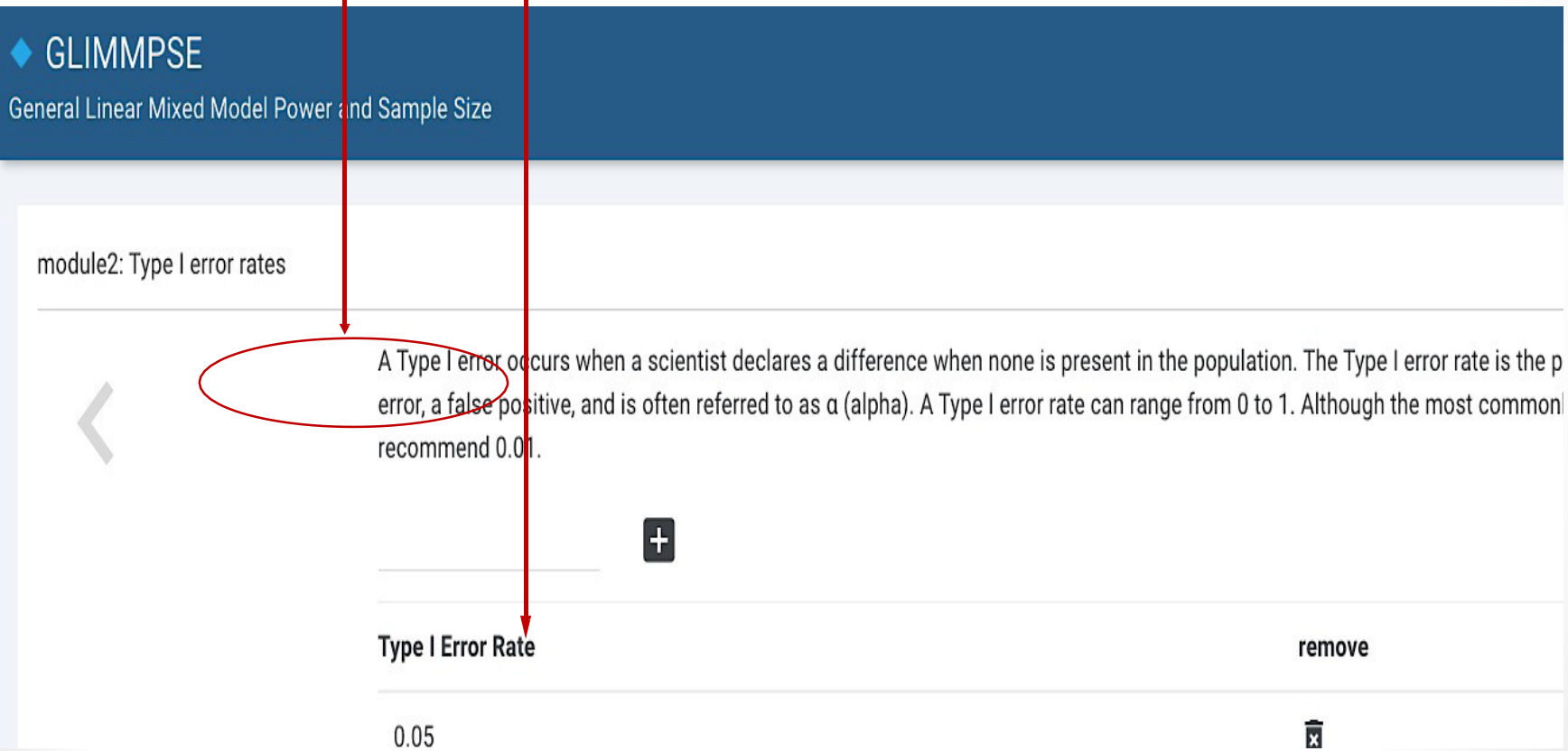
Hypothesis Test

We now move to select the hypothesis test of interest.
We click the Hotelling-Lawley trace (and align with the mixed model Wald test).



Now we choose the Type I error rate.

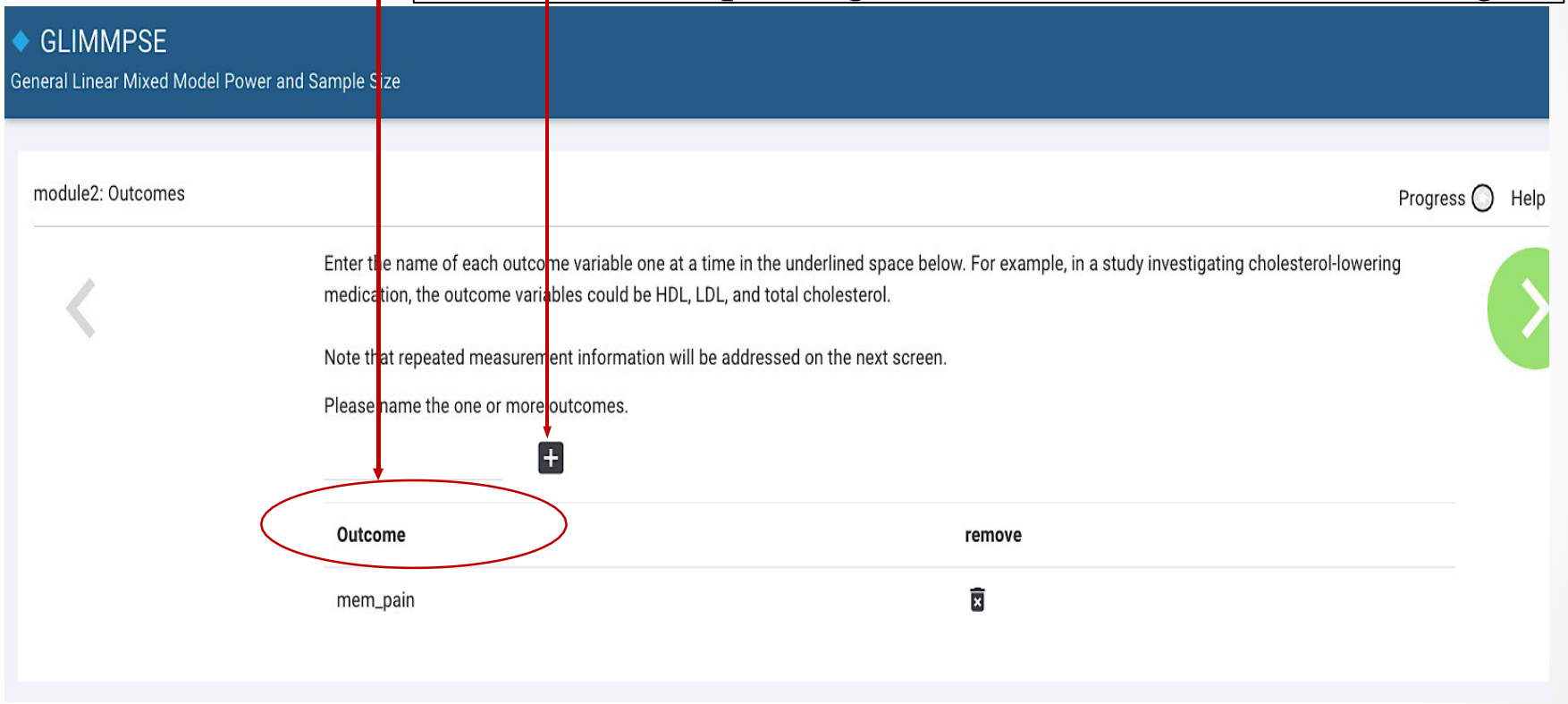
We type in 0.05 and click the plus sign to add this value.



One Outcome Variable

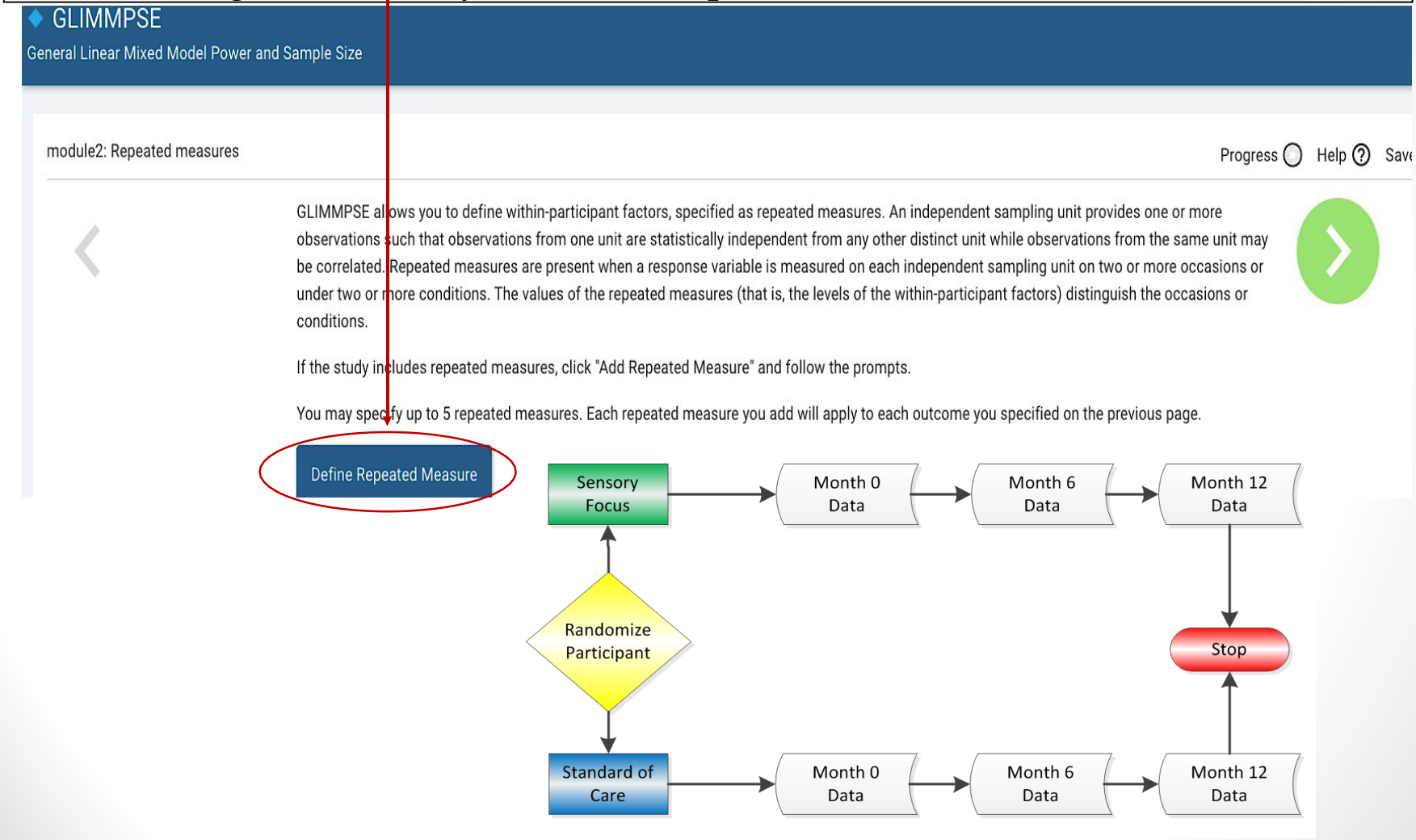
Enter outcome variables here.

Then, click the plus sign to add the outcome to the design.

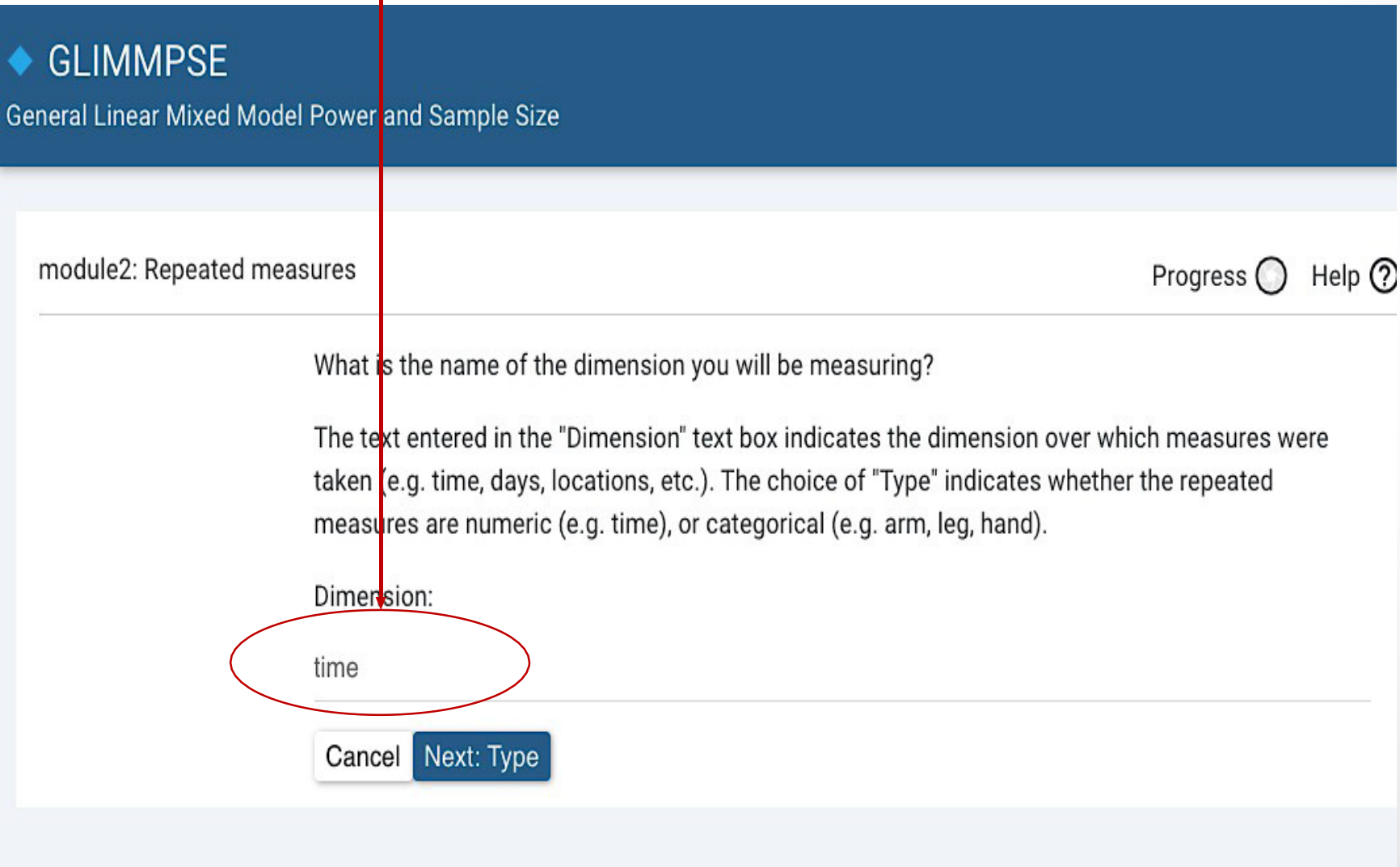


One Repeated Measures Dimension

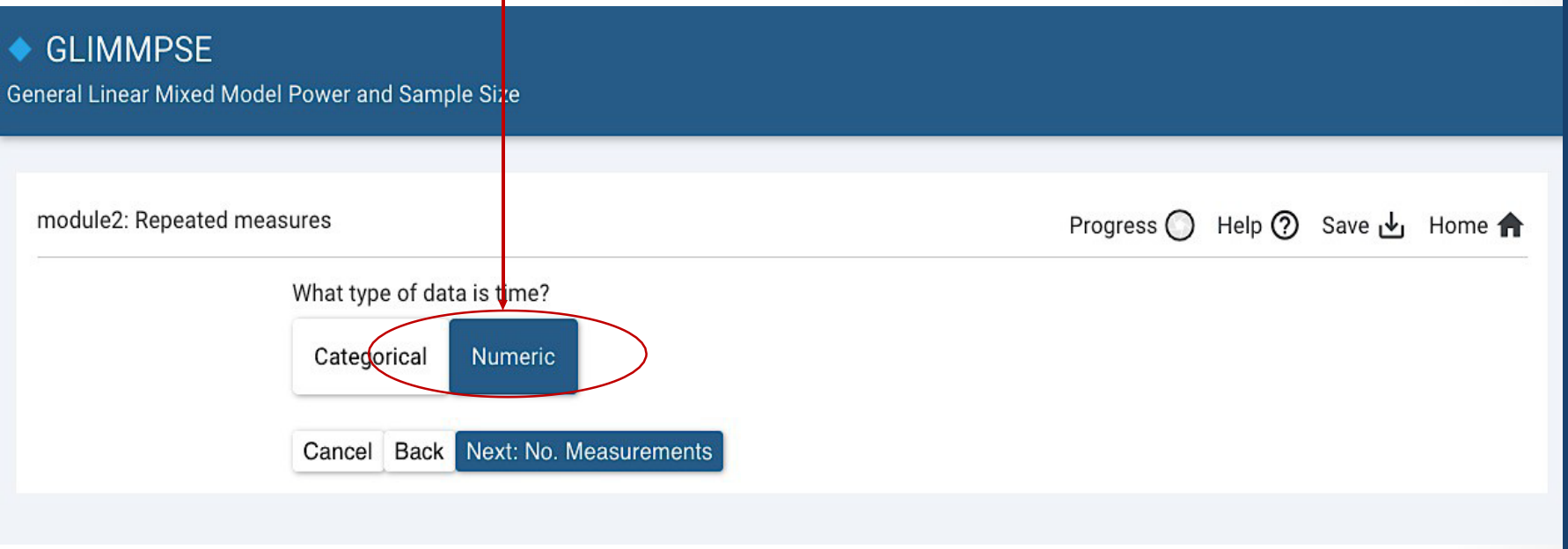
This is a longitudinal study with three repeated measurements of the outcomes.



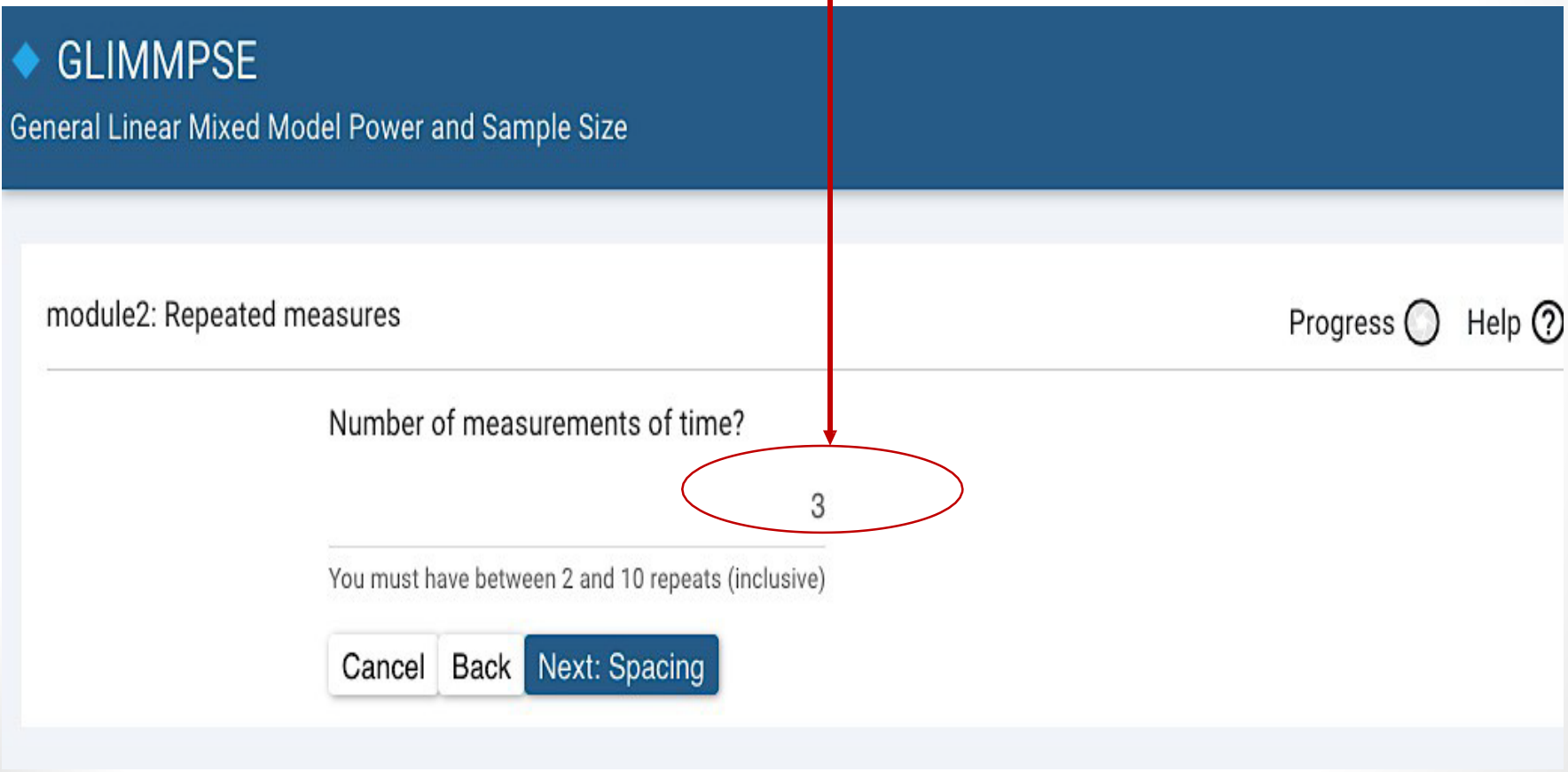
Here, we have named the dimension as time.



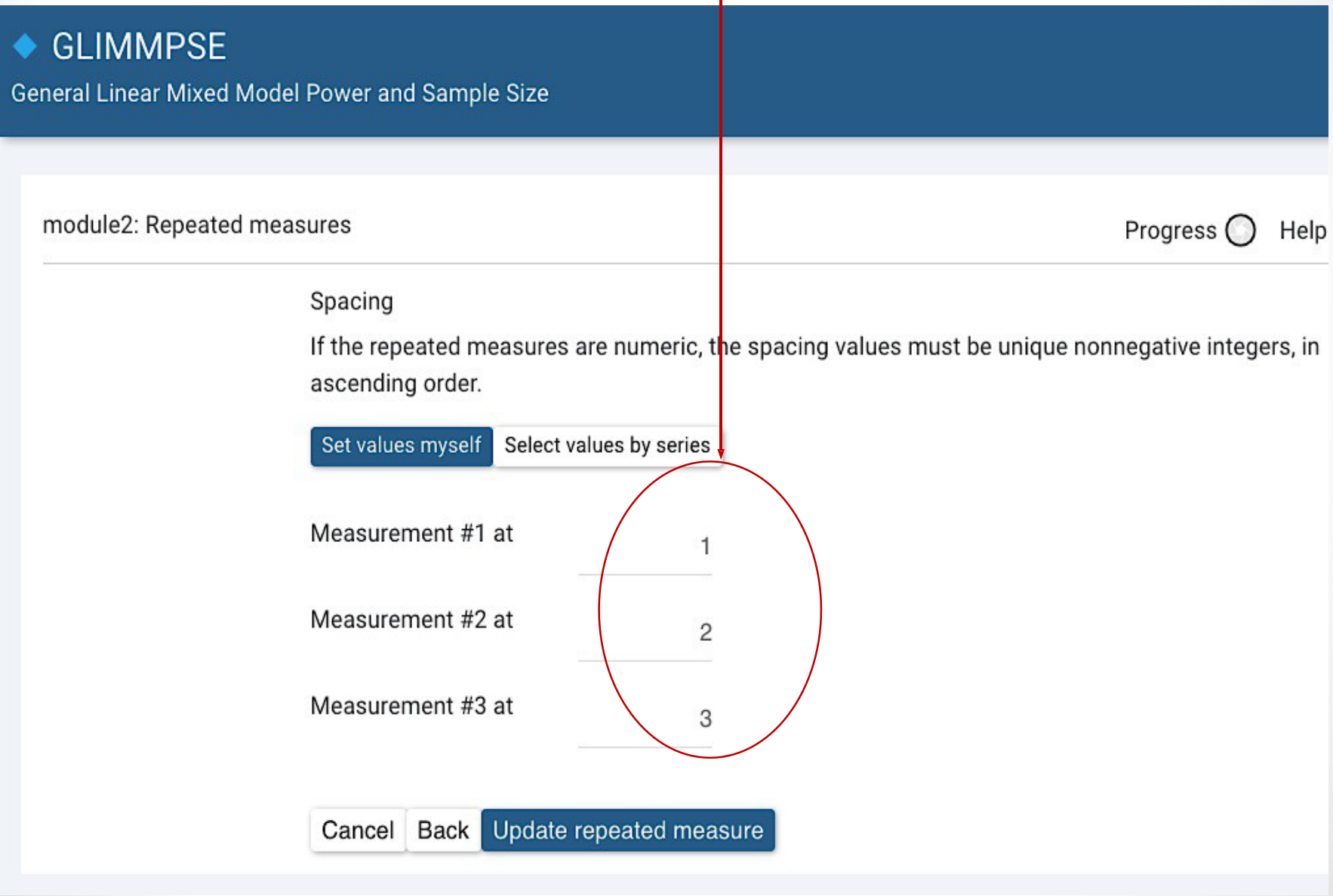
Here, we define the type of data that our dimension “time” represents.



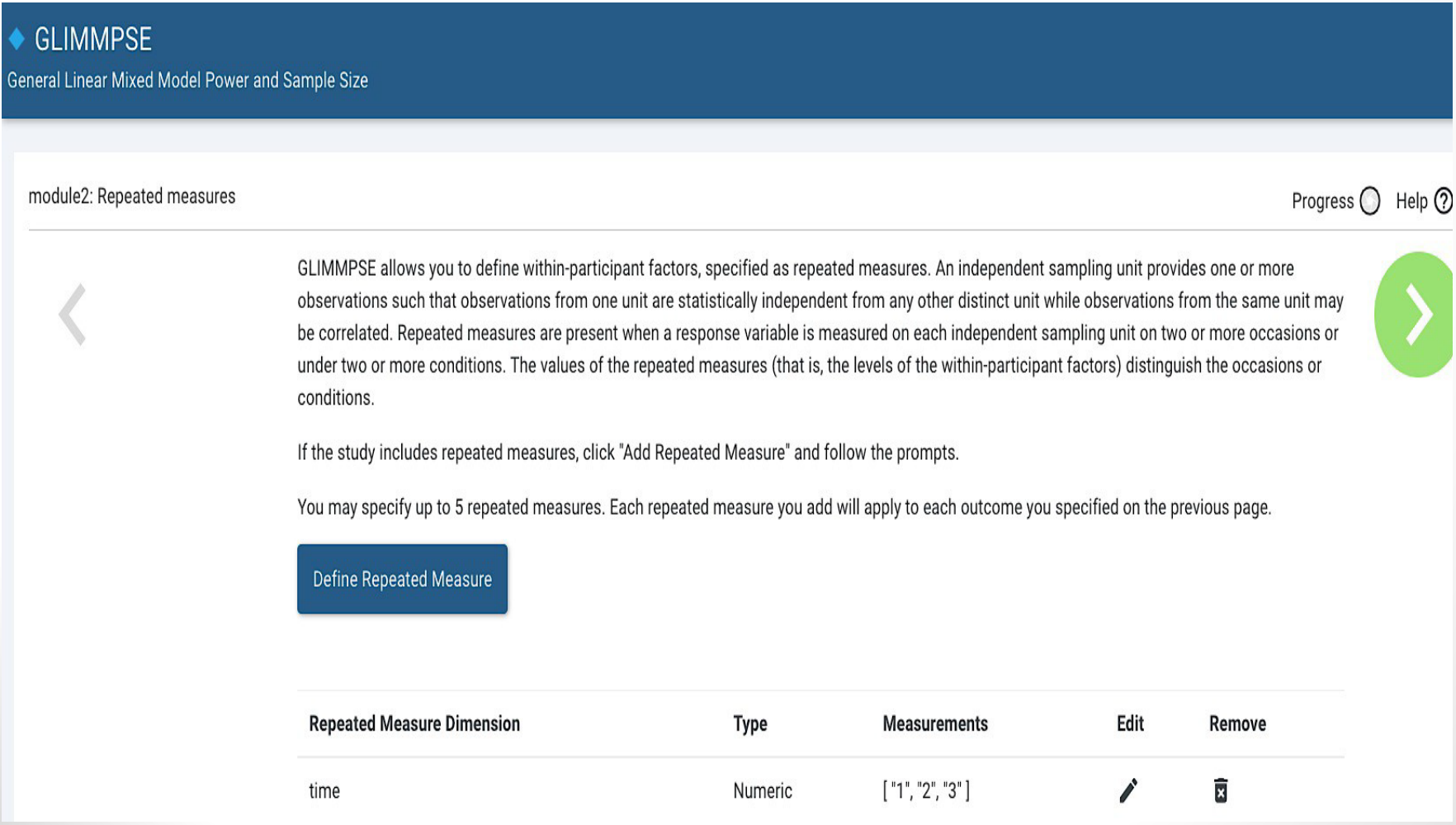
Enter the number of repeated measurements of the response variable.



Here, we enter the spacing values.

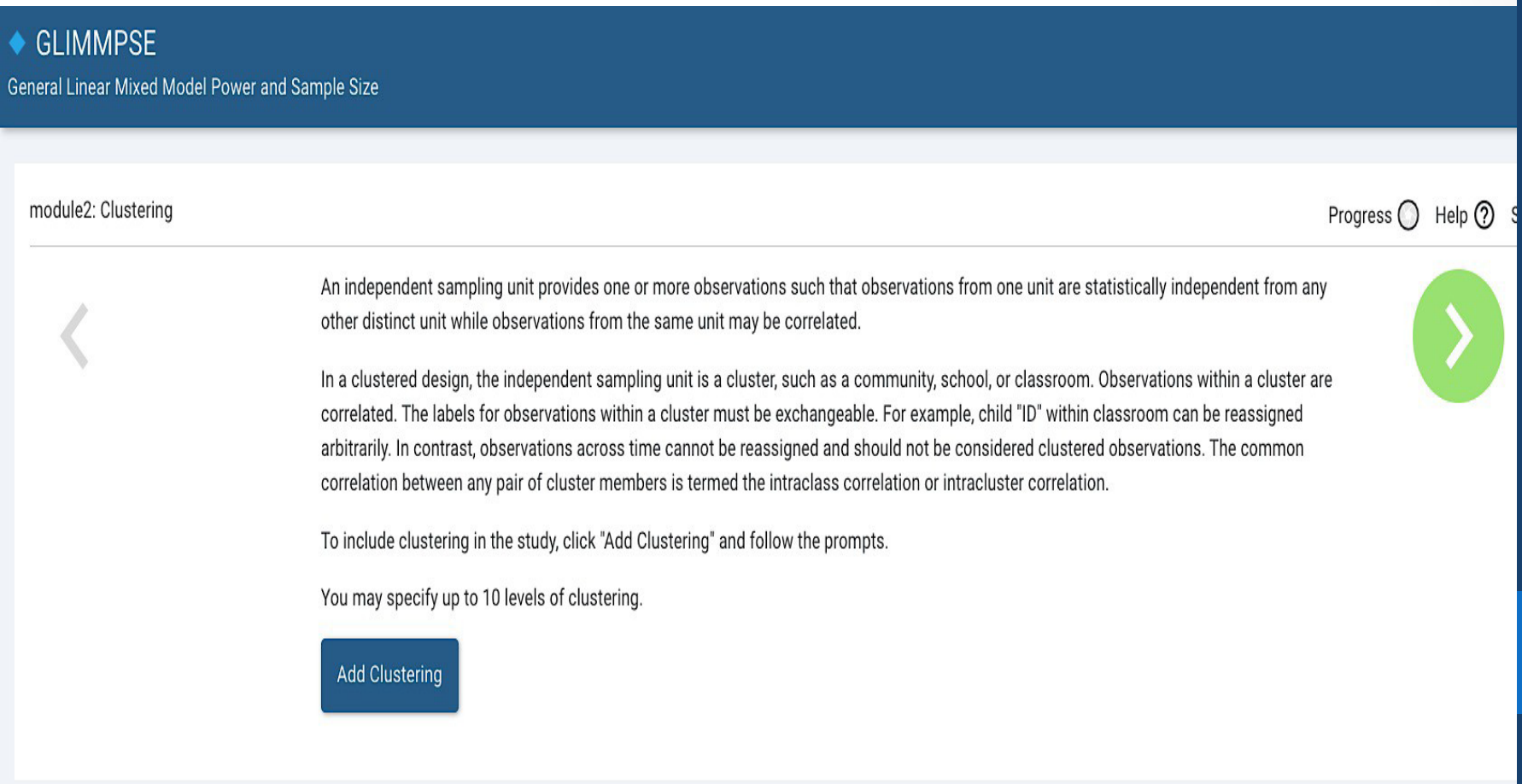


This screen summarizes the information entered for the repeated measures. GLIMMPSE can measure a given response variable up to 10 times.



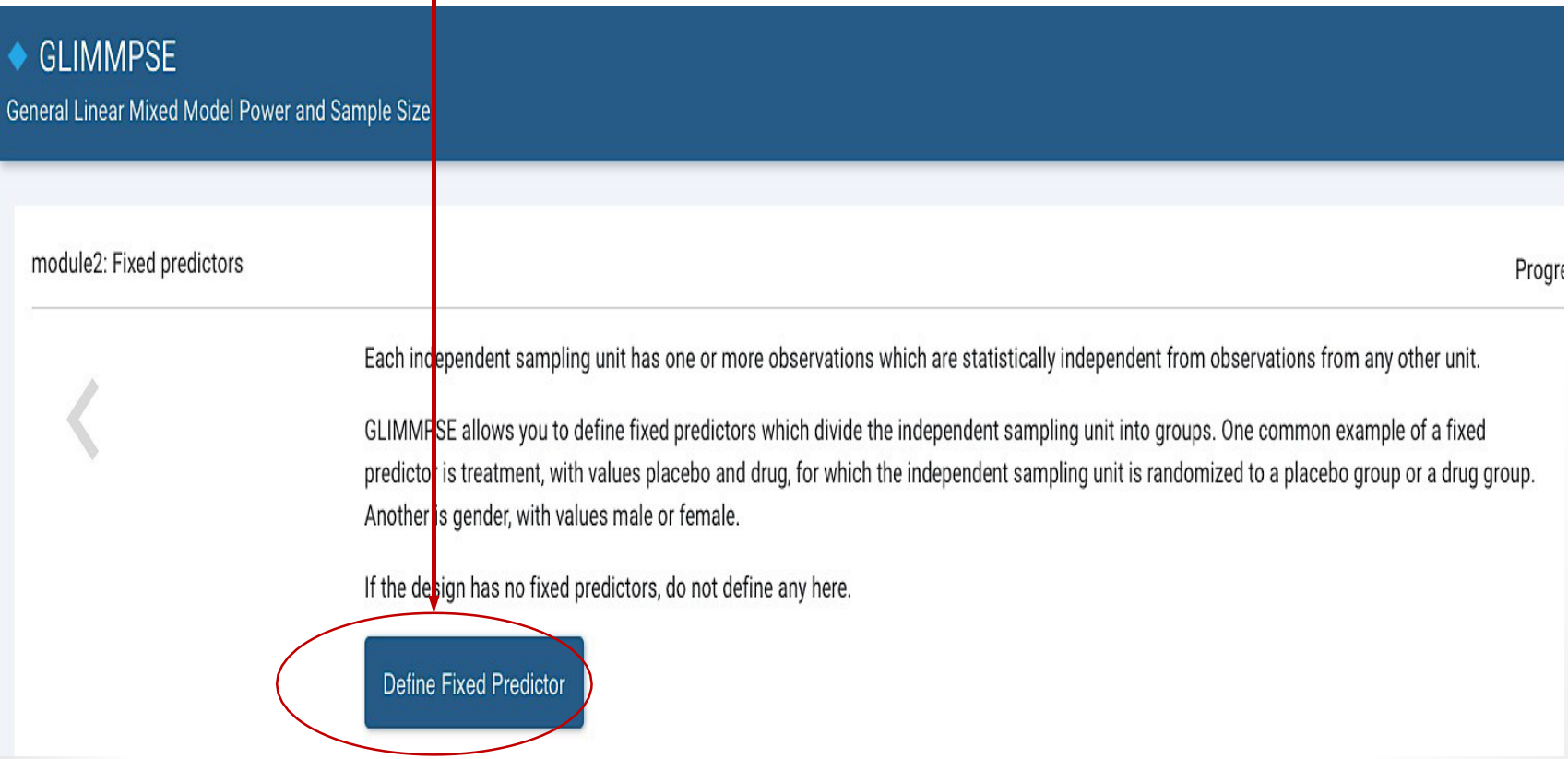
No Clustering in the Example

There is no clustering in this design, so we leave the clustering screen blank. GLIMMPSE allows up to 10 levels of clustering, with equal size clusters. Each level may have any size of cluster desired.

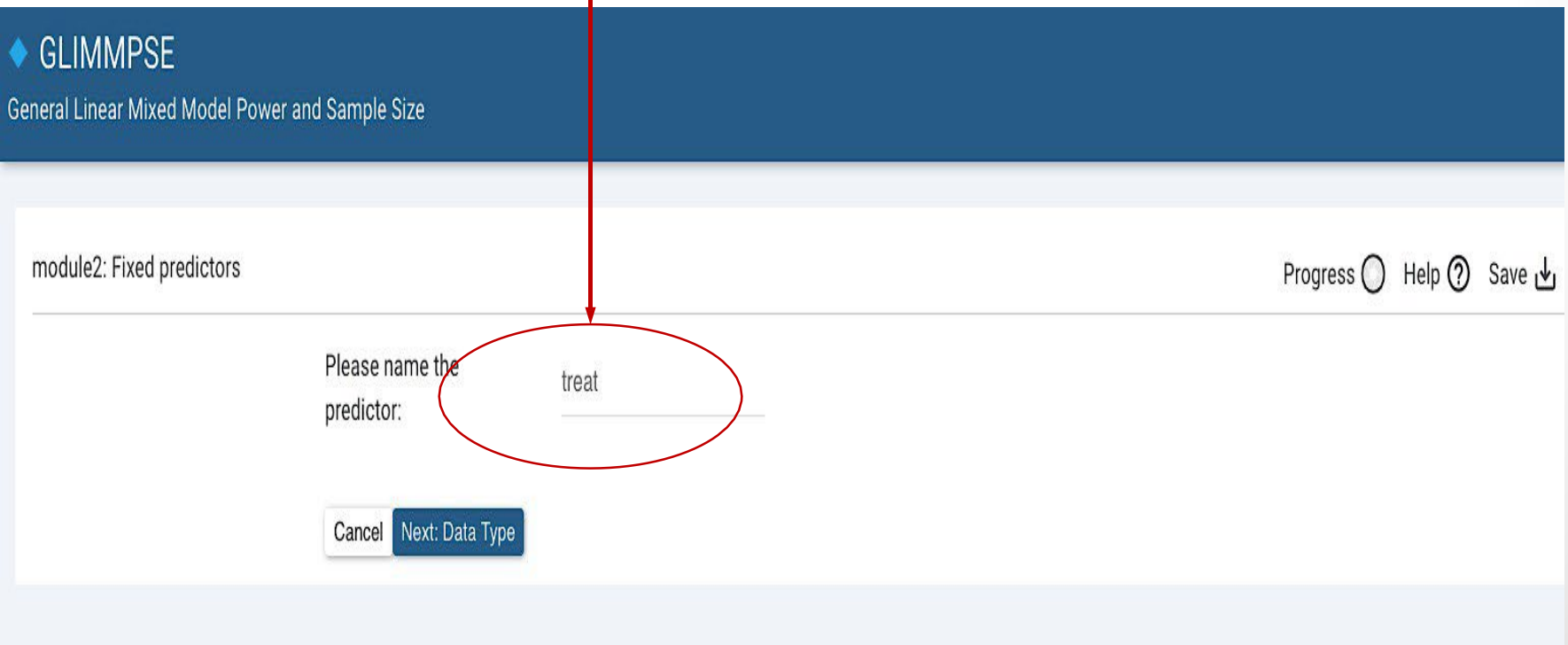


One Fixed Predictor

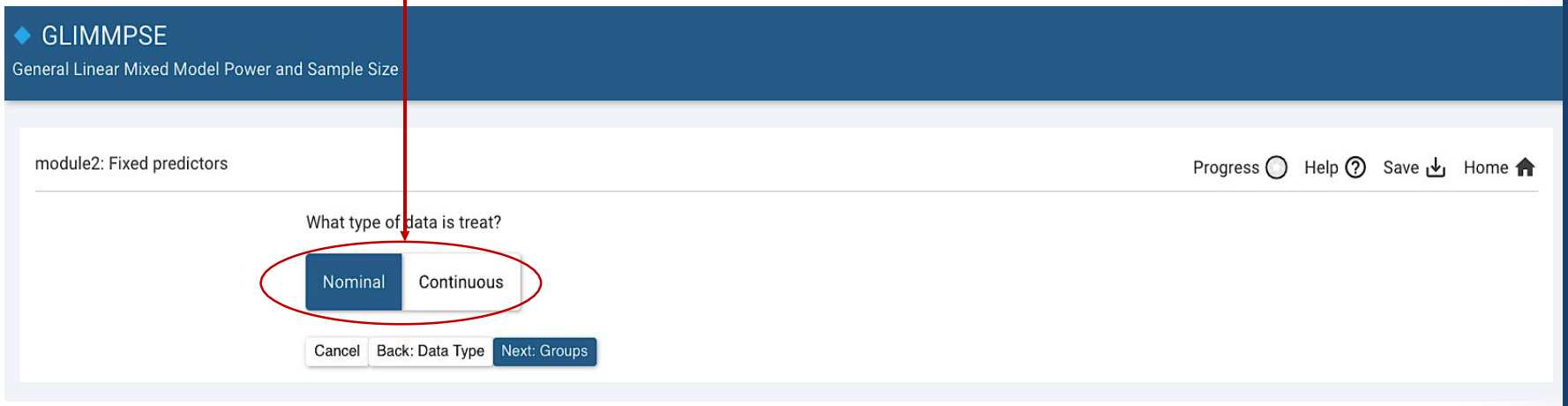
Here, we define the fixed predictor.



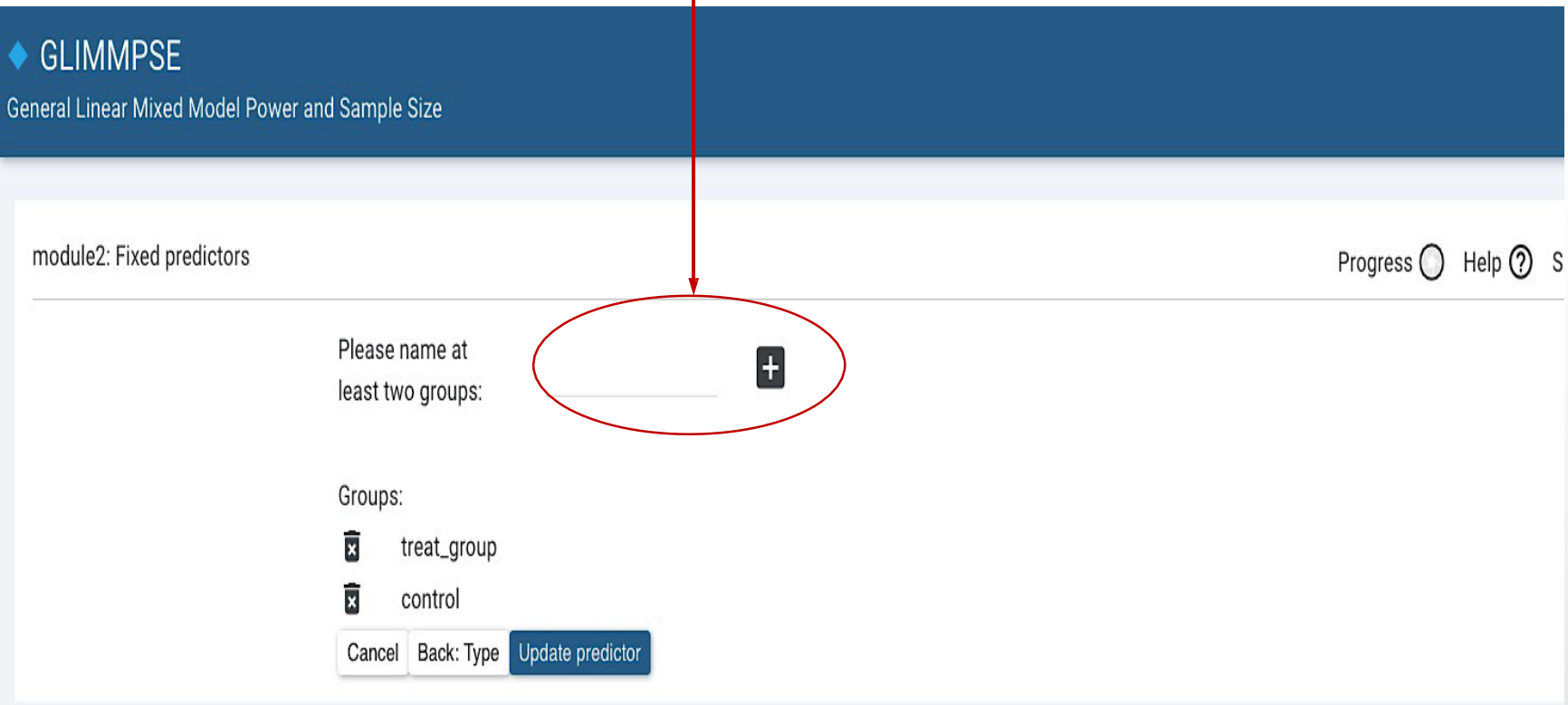
Now type in “treat" and hit enter. Predictor variables are the same thing as factors between independent sampling units.



Here, we define what type of data and move on to define the groups.

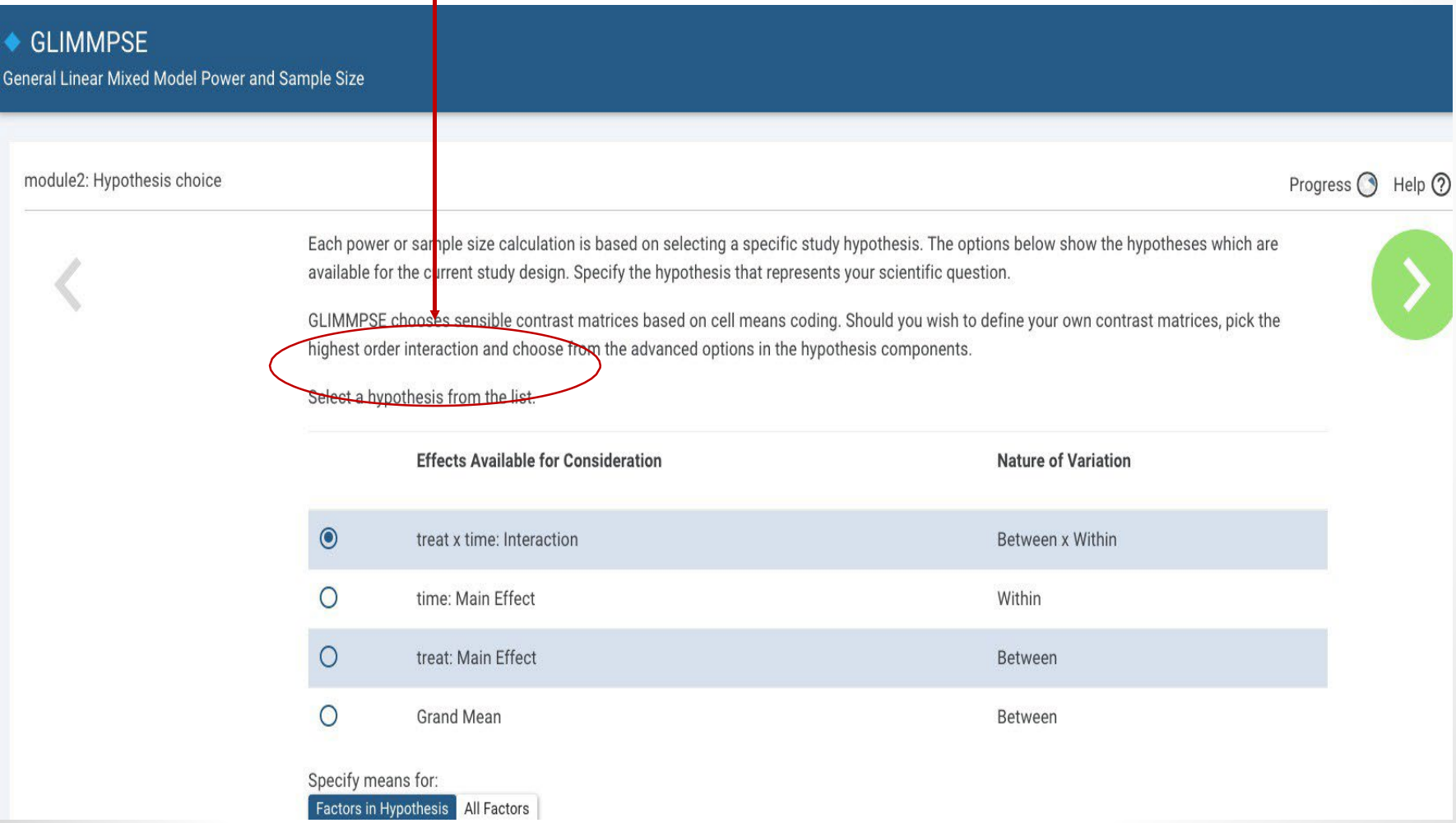


Here, we define the groups.



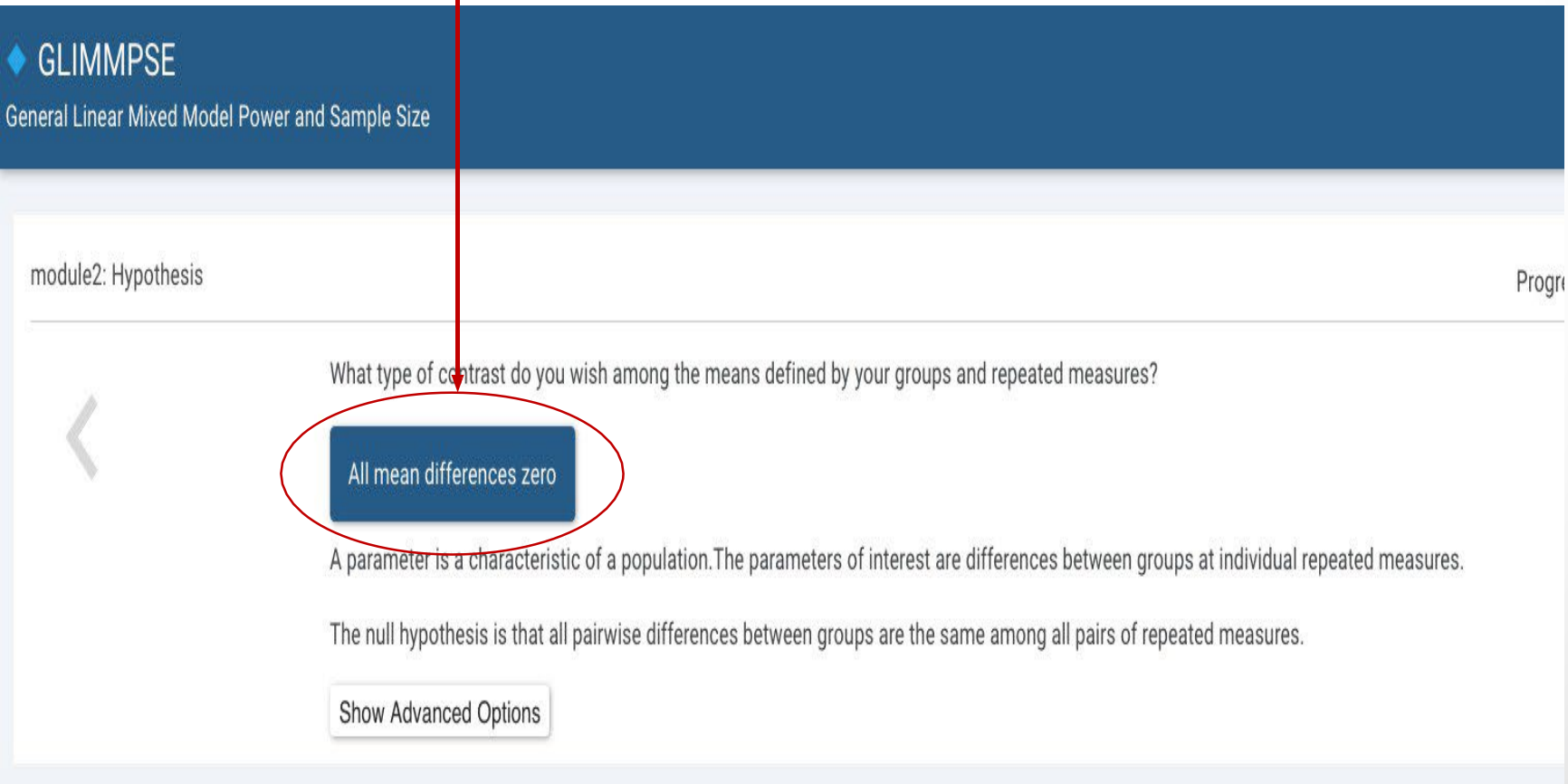
Choose the Contrast

The interaction hypothesis is a between-by-within independent sampling unit hypothesis, a time-by-predictor interaction.

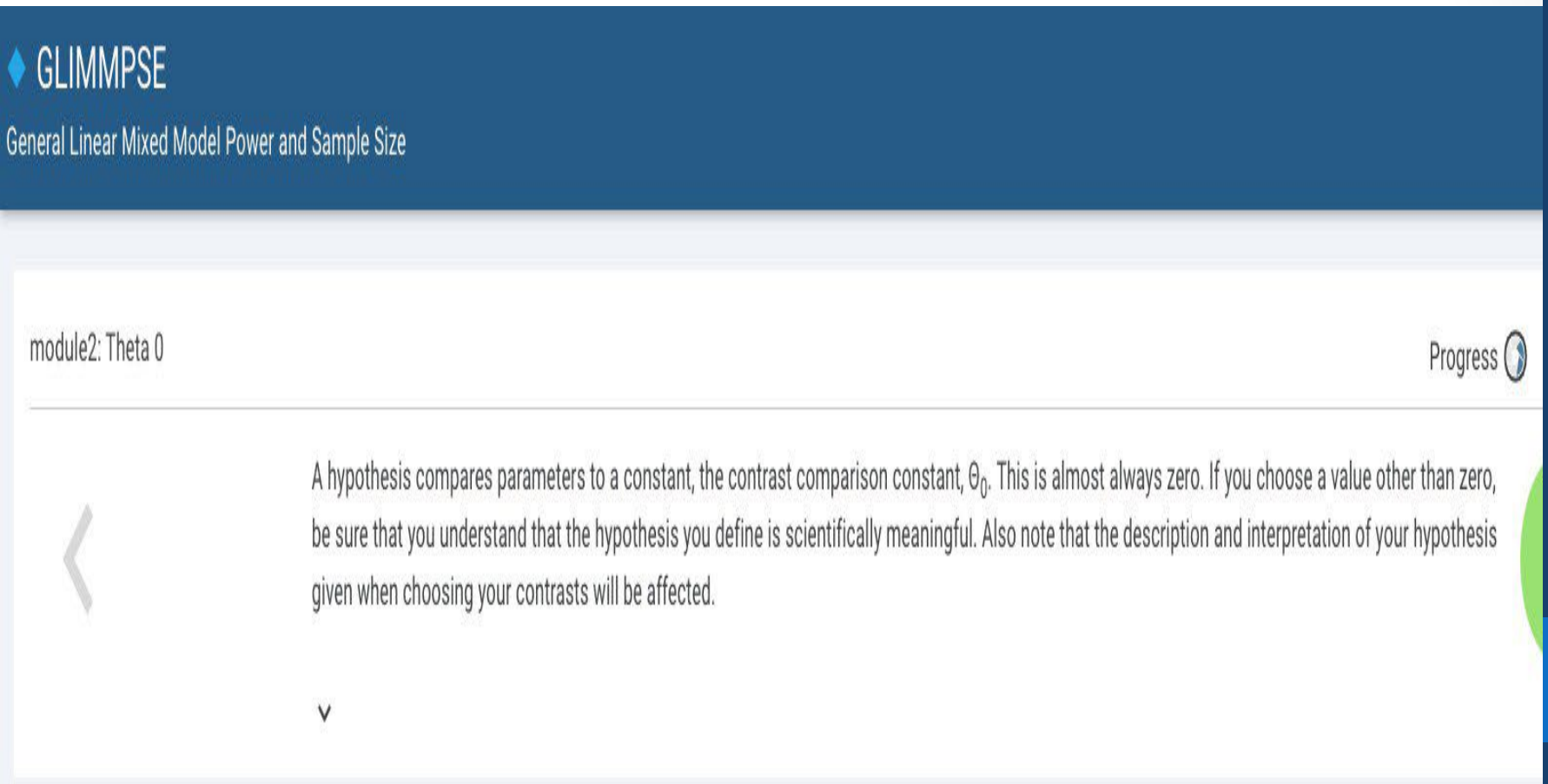


Standard or Custom Coefficients

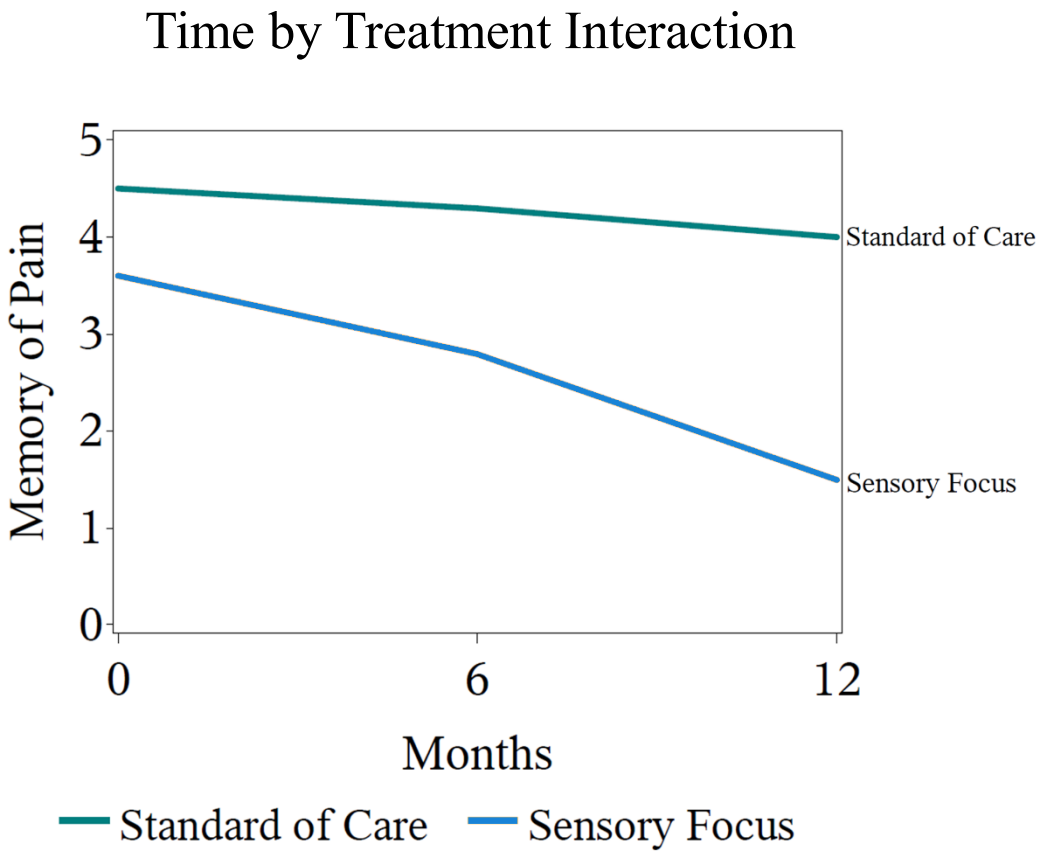
"All mean differences zero" was selected to indicate the type of contrast desired.



This screen gives you the option to select a value different than zero for the contrast comparison constant.

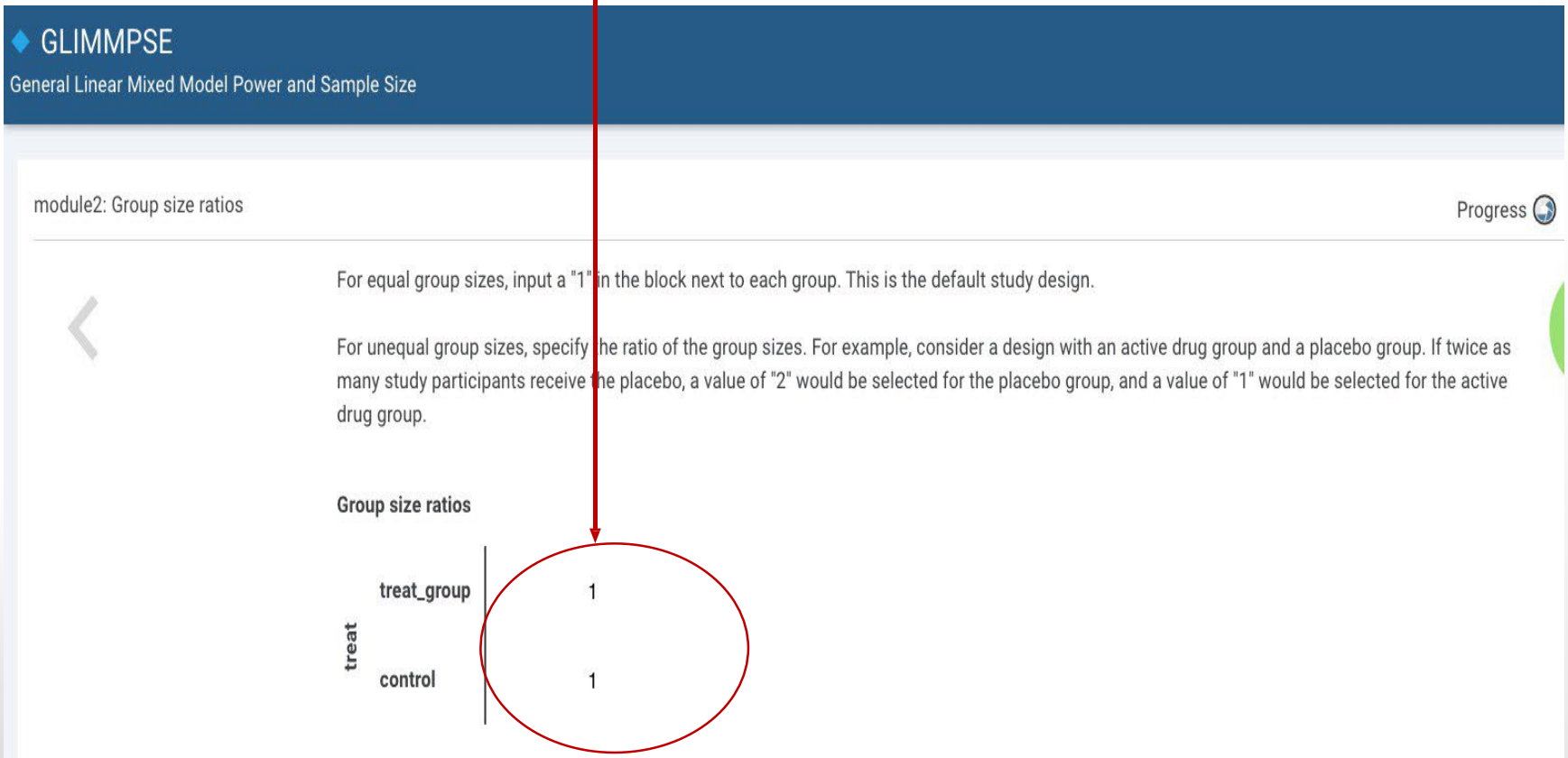


Hypothesis


Time by Treatment Interaction
Memory of Pain
5
4
3
2
1
0
0
6
12
Months
Standard of Care
Sensory Focus
Standard of Care
Sensory Focus

Fixed Predictor
Relative Group Sizes

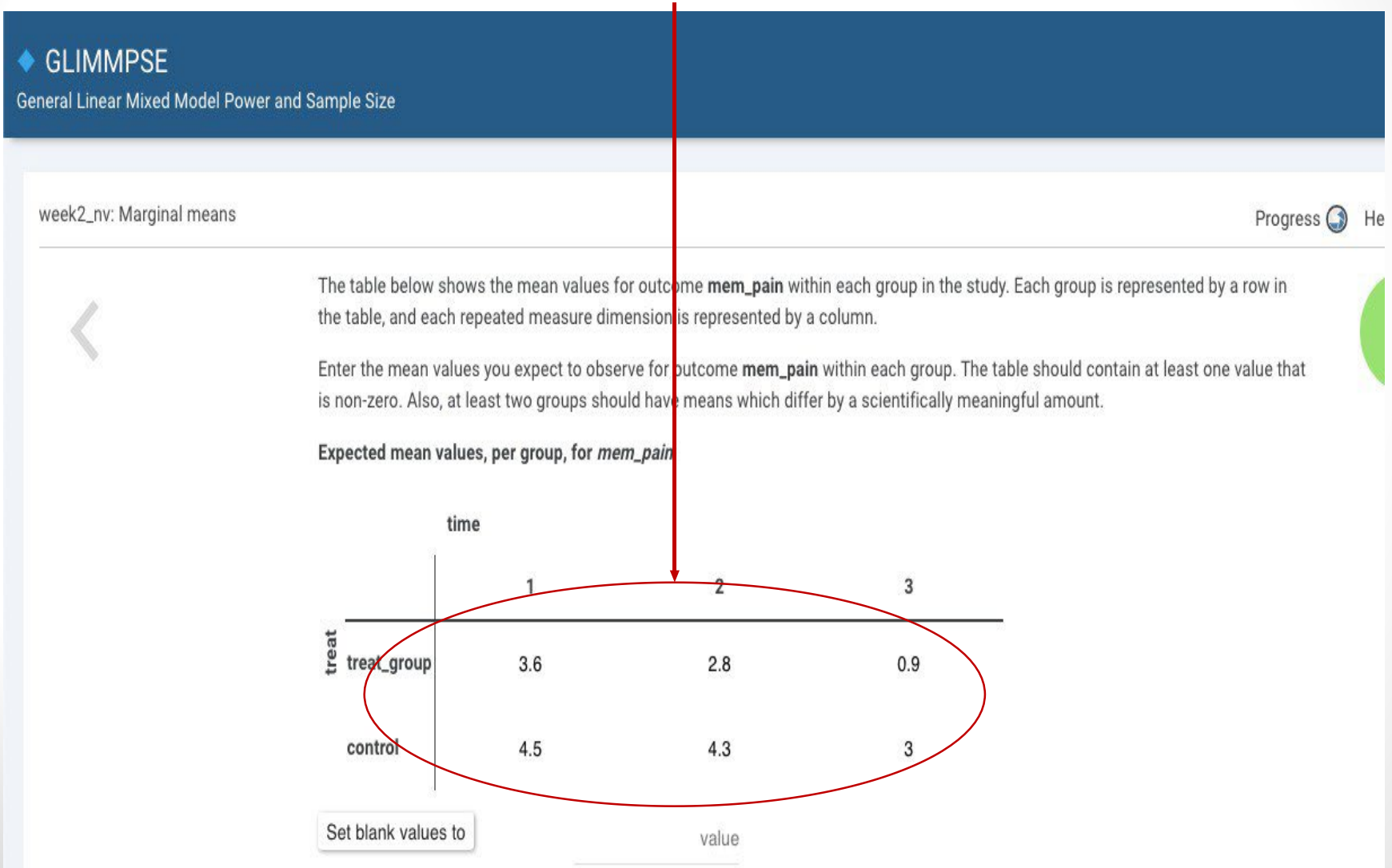
Study participants are equally randomized to the two levels of treatment of equal size: sensory focus (treat) and standard of care (control).



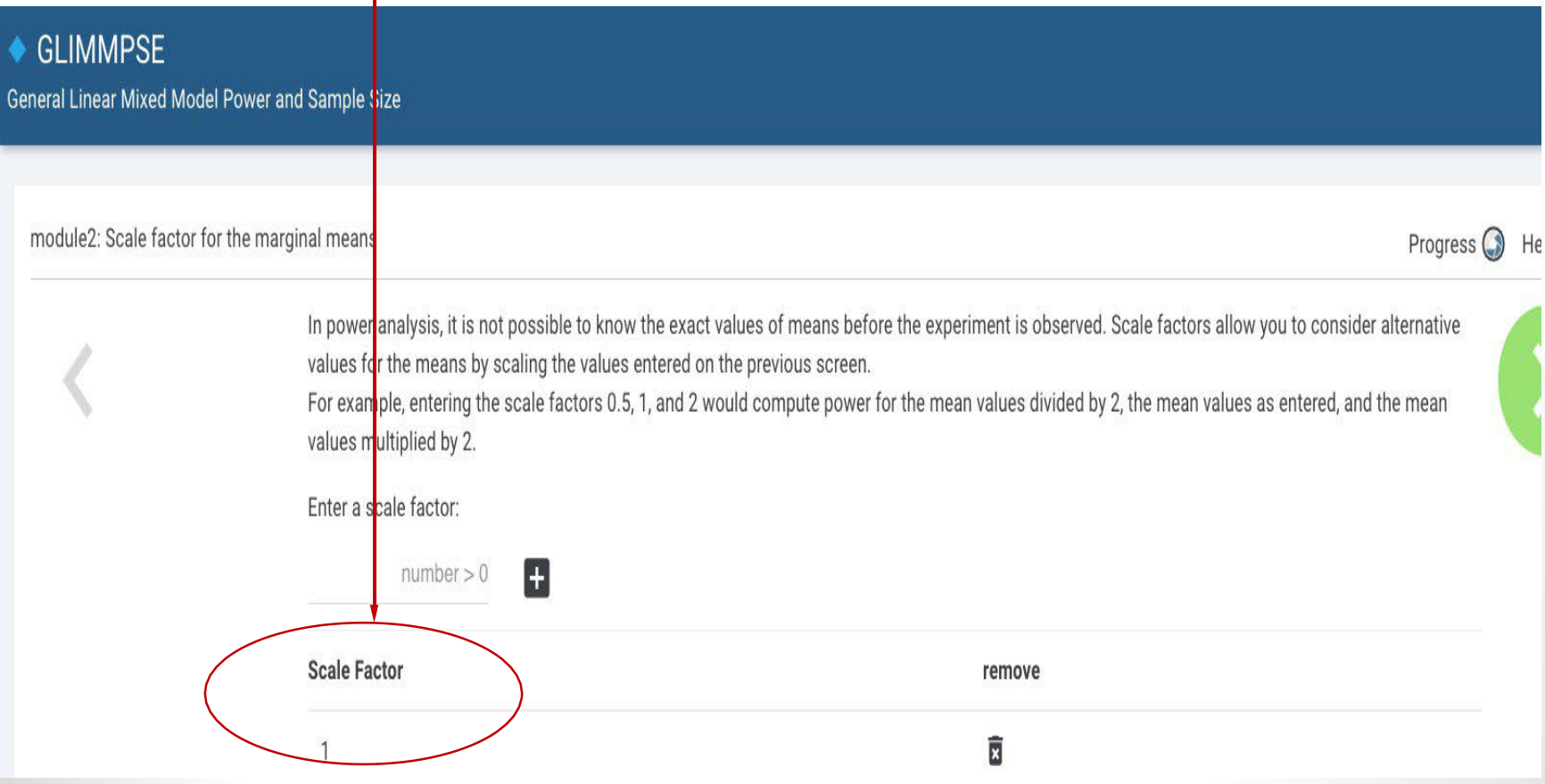
Means

Intervention	Baseline	6 Months	12 Months
Sensory Focus (SF)	3.6	2.8	0.9
Standard of Care (SOC)	4.5	4.3	3.0
Intervention Difference (SF - SOC)	0.9	1.5	-2.1
Net Difference Over Time (12 Months - Baseline)			-1.2

Enter the mean values for the outcome variable within each group as shown.



Often it is useful to consider mean differences larger or smaller than our initial guess. Here we type in 1 to indicate that our initial guess is correct.
The Scale Factors option is one way of 'Accounting for Uncertainty.'



Variances and Correlations

- Consider the sources of variability and correlation in the study design.
  - Repeated measures **within a given participant** will be correlated.
  - Outcome measurements will vary **between participants**.

Variances and Correlations

Correlation Between Outcomes Over Time

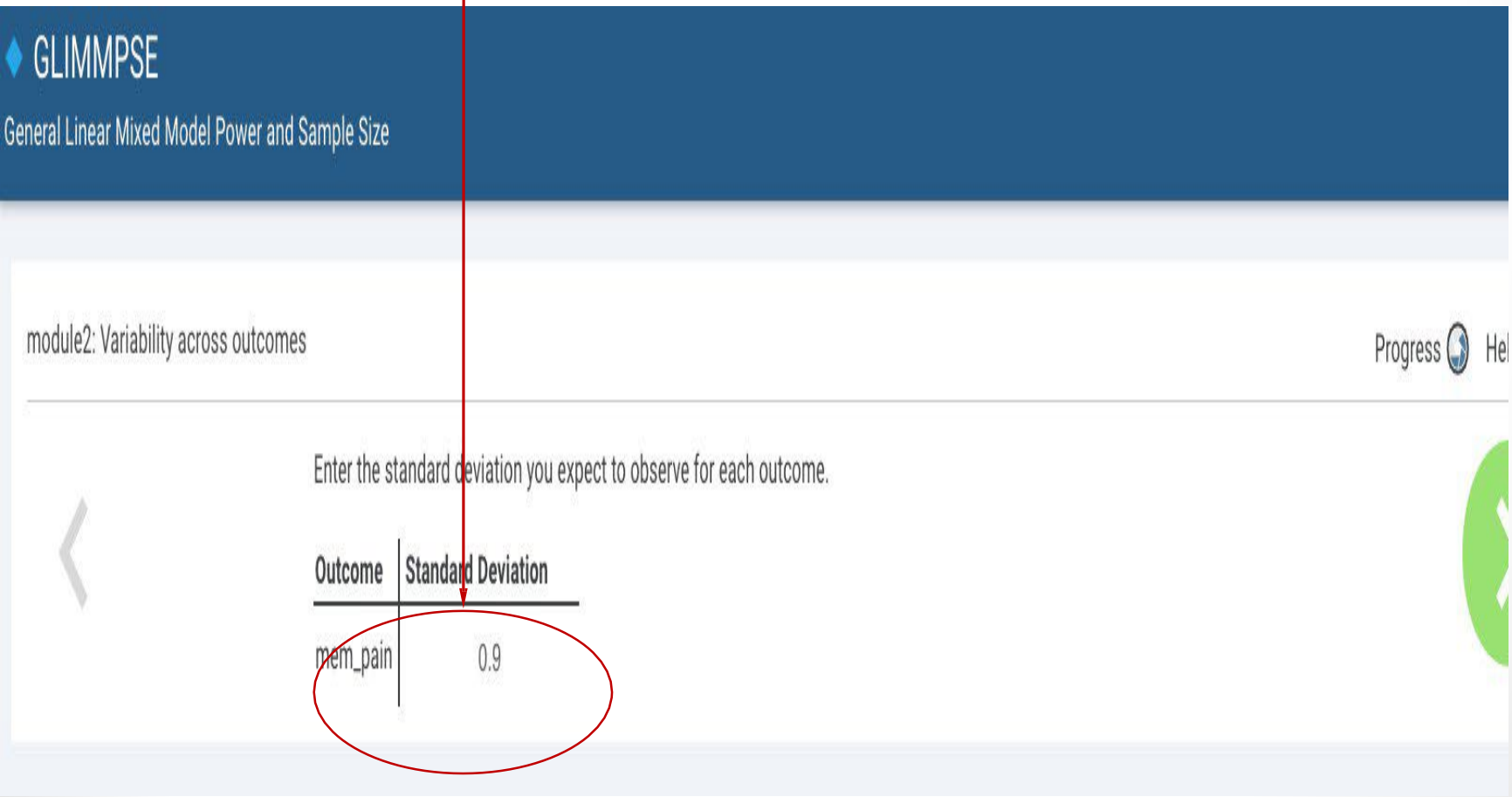
Gedney, Logan, and Baron (2003) identified predictors of the amount of experienced pain recalled over time…One of the findings was that memory of pain intensity at 1 week and 18 months had a correlation of 0.406. We assume that the correlation between measures 18 months apart will be similar to the correlation between measures 12 months apart. Likewise, the correlation between measures 6 months apart will be only slightly greater than the correlation between measures 18 months apart.

Variances and Correlations

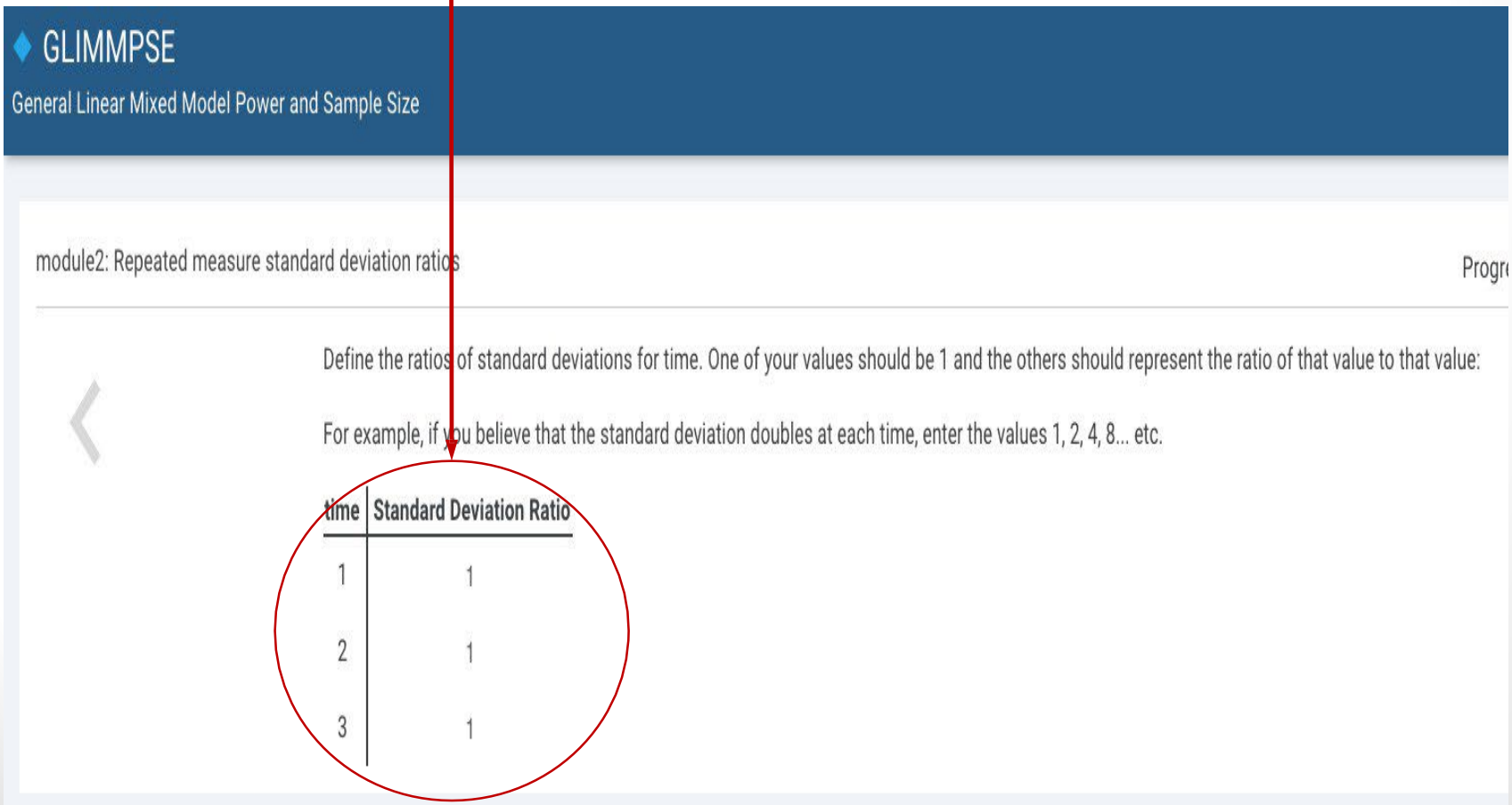
Standard Deviation of the Outcome

Logan, et al. (1995) examined whether sensory focus therapy during a root canal procedure could reduce a patient's experienced pain. The investigators assessed experienced pain on a 5 point scale both immediately and at one week following the procedure. The standard deviation of the measurements was 0.90.

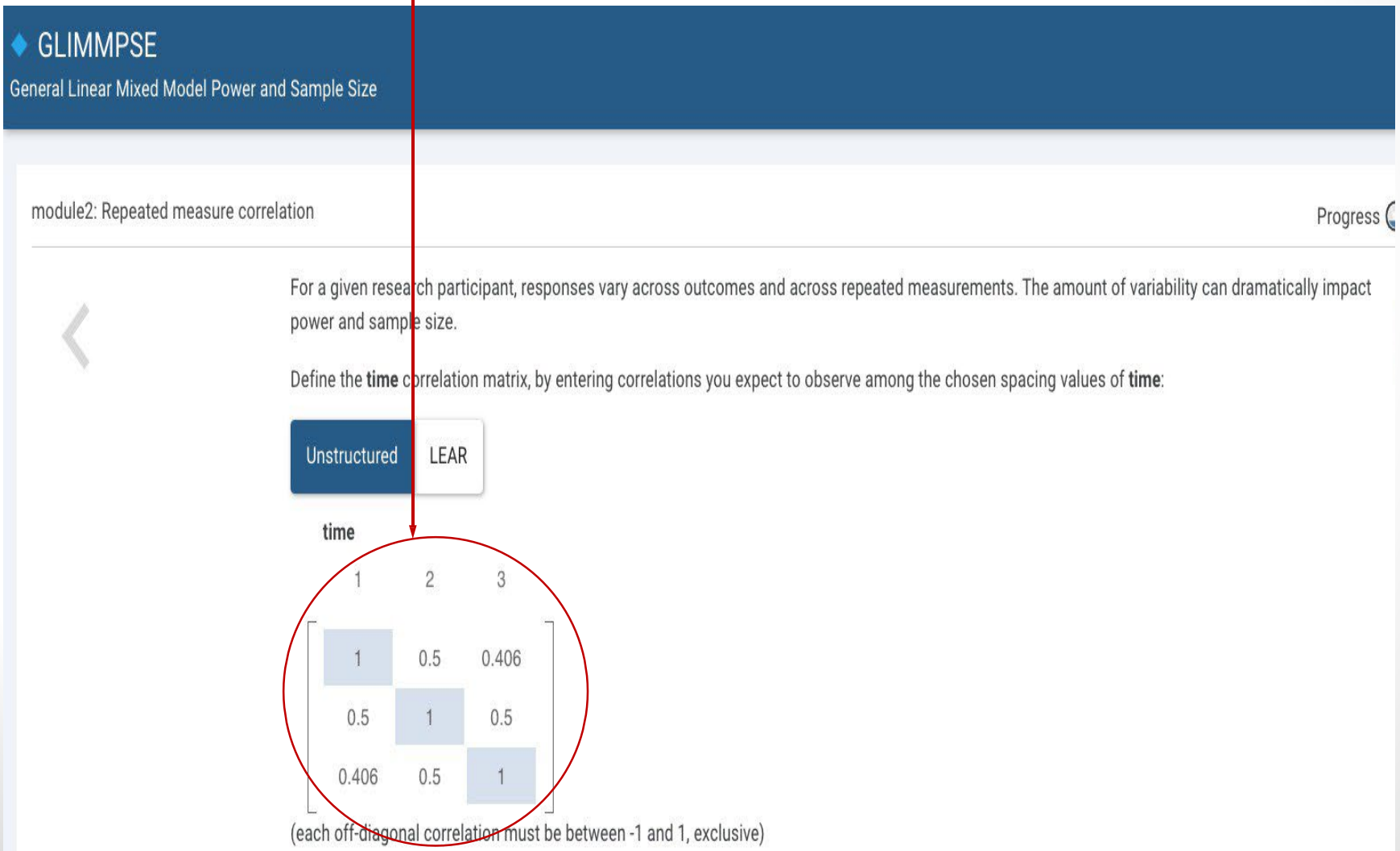
Enter the standard deviation as shown.



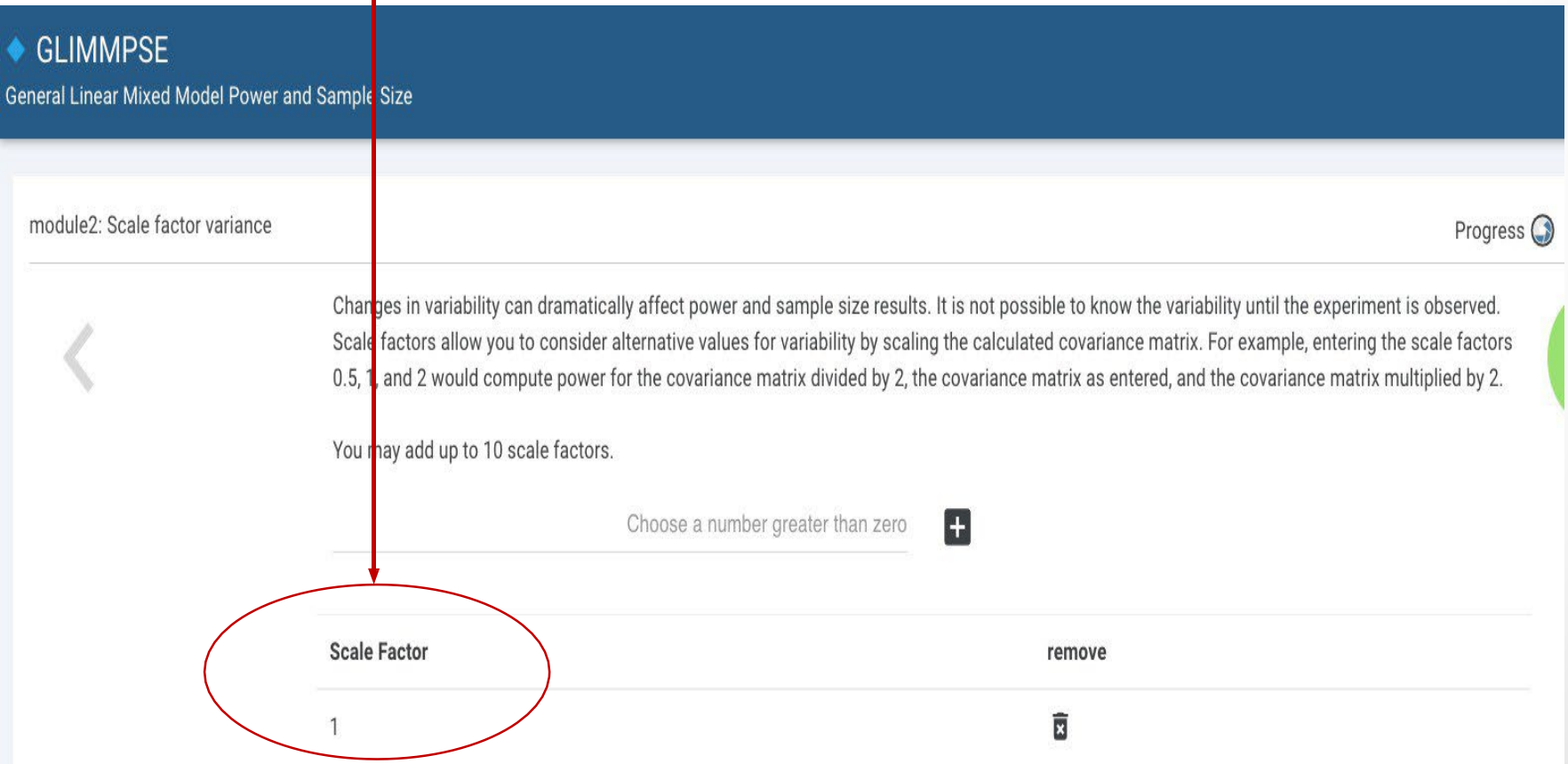
Enter the ratios of standard deviations for time.



Enter the correlations you expect to observe as shown below.

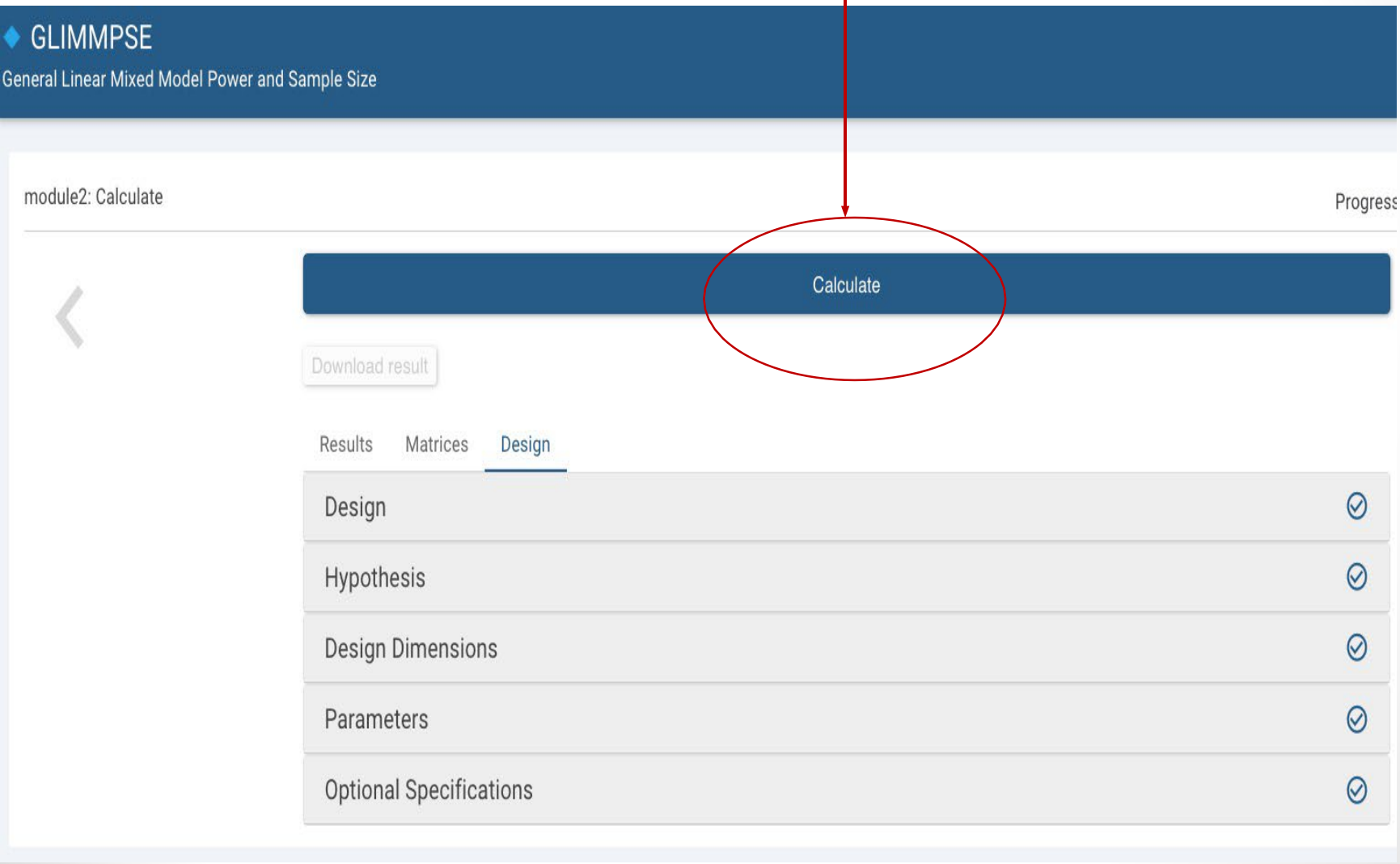


Because we have good evidence from the previous study for the variability and correlation, we enter 1 for the scale factor as shown below.



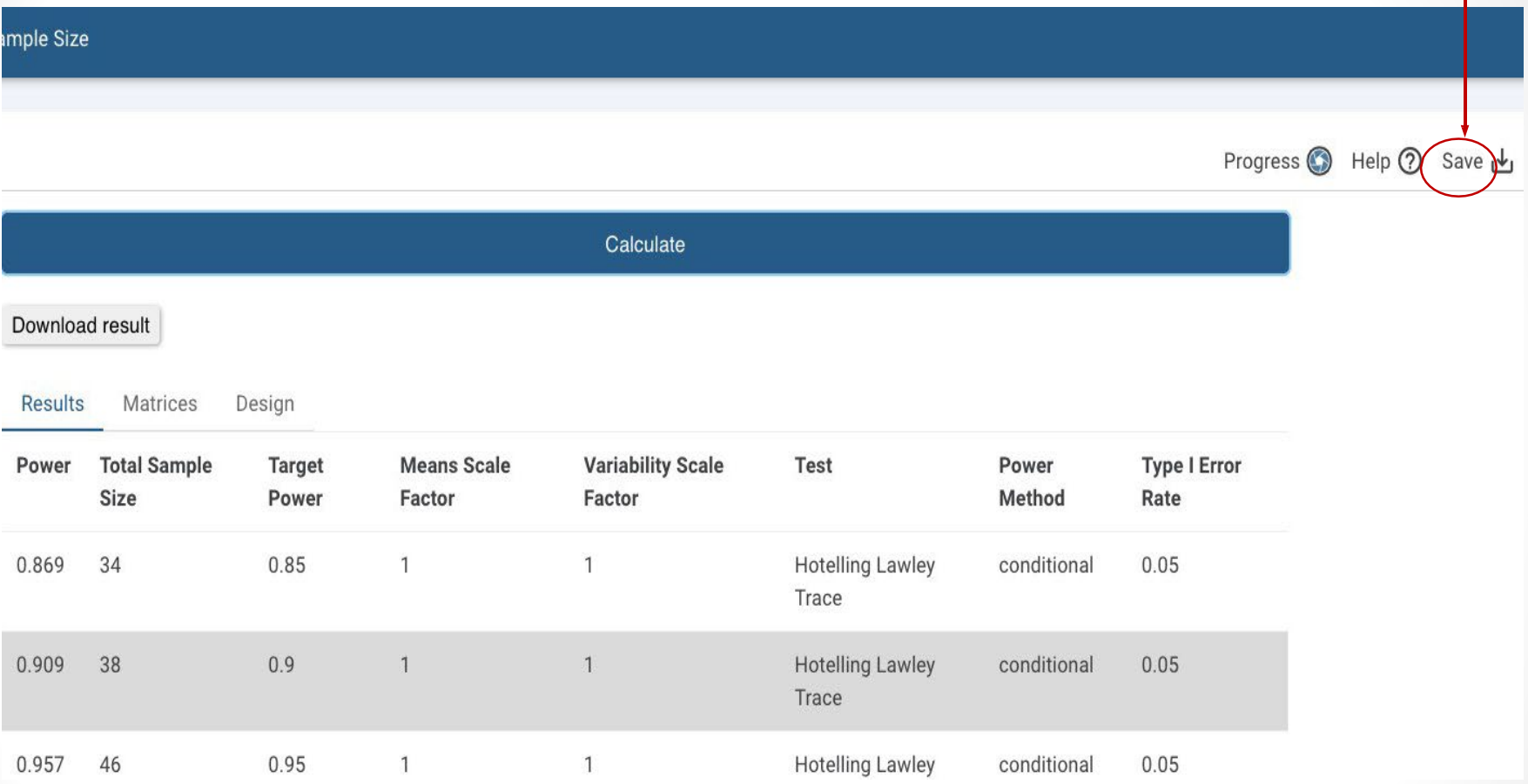
Study Defined; Ready to Compute

After we hit the "Calculate" button, the results will be shown in a table.



Save Results and .json Files

We can save results and study design inputs by using the "Save" button.



Power	Total Sample Size	Target Power	Means Scale Factor	Variability Scale Factor	Test	Power Method	Type I Error Rate
0.869	34	0.85	1	1	Hotelling Lawley Trace	conditional	0.05
0.909	38	0.9	1	1	Hotelling Lawley Trace	conditional	0.05
0.957	46	0.95	1	1	Hotelling Lawley	conditional	0.05

We sought sample sizes to give "Target" powers of at least 0.85, 0.9, and 0.95.
Actual powers are 0.869, 0.909 and 0.957.
Sample size is discrete. We need an even sample size for two equal size groups.

Here are the matrices that were used for the calculation.

Results | Matrices | Design

$$Es(\mathbf{X}) = \begin{bmatrix} 1.00 & 0.00 \\ 0.00 & 1.00 \end{bmatrix}$$

$$\mathbf{B} = \begin{bmatrix} 3.60 & 2.80 & 0.900 \\ 4.50 & 4.30 & 3.00 \end{bmatrix}$$

$$\mathbf{C} = \begin{bmatrix} 1.00 & -1.00 \end{bmatrix}$$

$$\mathbf{U} = \begin{bmatrix} 1.00 & 1.00 \\ -1.00 & 0.00 \\ 0.00 & -1.00 \end{bmatrix}$$

$$\mathbf{\Sigma}_\star = (\mathbf{U}_o' \mathbf{\Sigma}_o \mathbf{U}_o) \otimes (\mathbf{U}_r' \mathbf{\Sigma}_r \mathbf{U}_r) \otimes (\mathbf{U}_c' \mathbf{\Sigma}_c \mathbf{U}_c)$$

$$= [0.810] \otimes \begin{bmatrix} 1.00 & 0.594 \\ 0.594 & 1.19 \end{bmatrix} \otimes [1.00] = \begin{bmatrix} 0.810 & 0.481 \\ 0.481 & 0.962 \end{bmatrix}$$

$$\mathbf{\Theta}_0 = \begin{bmatrix} 0.00 & 0.00 \end{bmatrix}$$

$$\alpha = 0.05$$

$$\mathbf{\Theta} = \begin{bmatrix} 0.600 & 1.20 \end{bmatrix}$$

$$\mathbf{M} = [2.00]$$

$$\nu_e = 2$$

No. of replicated rows in design matrix: 1

$$Es(\mathbf{\Delta}) = \begin{bmatrix} 0.180 & 0.360 \\ 0.360 & 0.720 \end{bmatrix}$$

Sample Size Calculation Summary

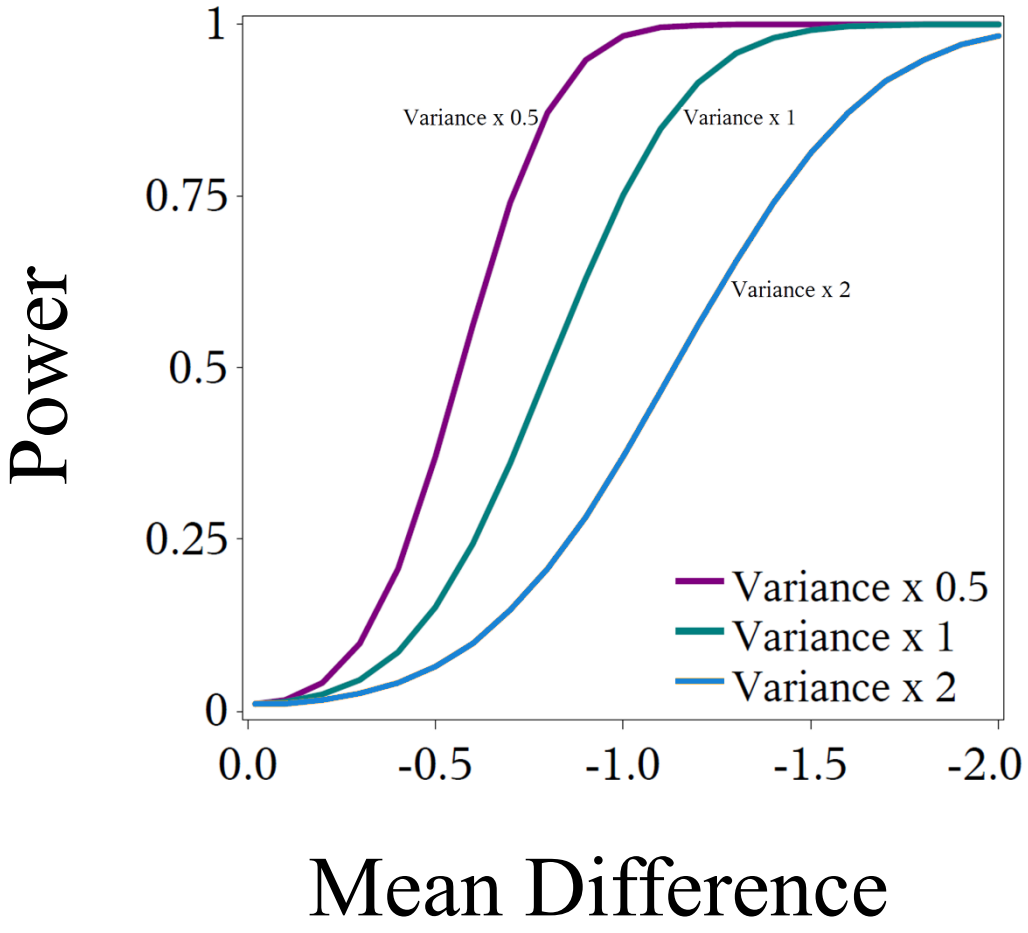
We plan a repeated measures analysis using the Wald (Hotelling-Lawley) statistic to test for a time by treatment interaction.

Based on previous studies, we predict memory of pain measures will have a standard deviation of 0.90 and the correlation between baseline and 6 months will be 0.5.

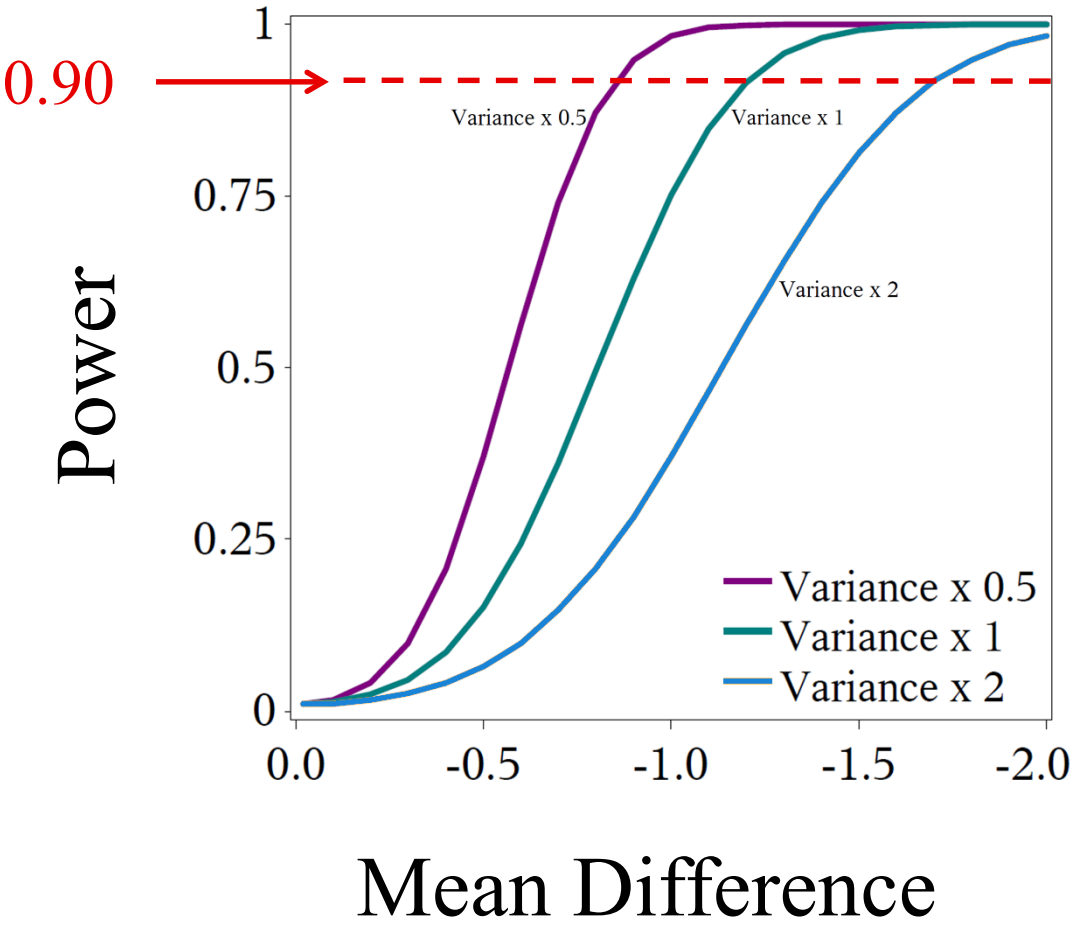
Based on previous studies, we believe the correlation will decrease slowly over time, for a correlation of 0.406 between pain recall measures at baseline and 12 months.

For a desired power of 0.90 and a Type I error rate of 0.05, we estimated that we would need 38 participants to detect a mean difference of 1.2.

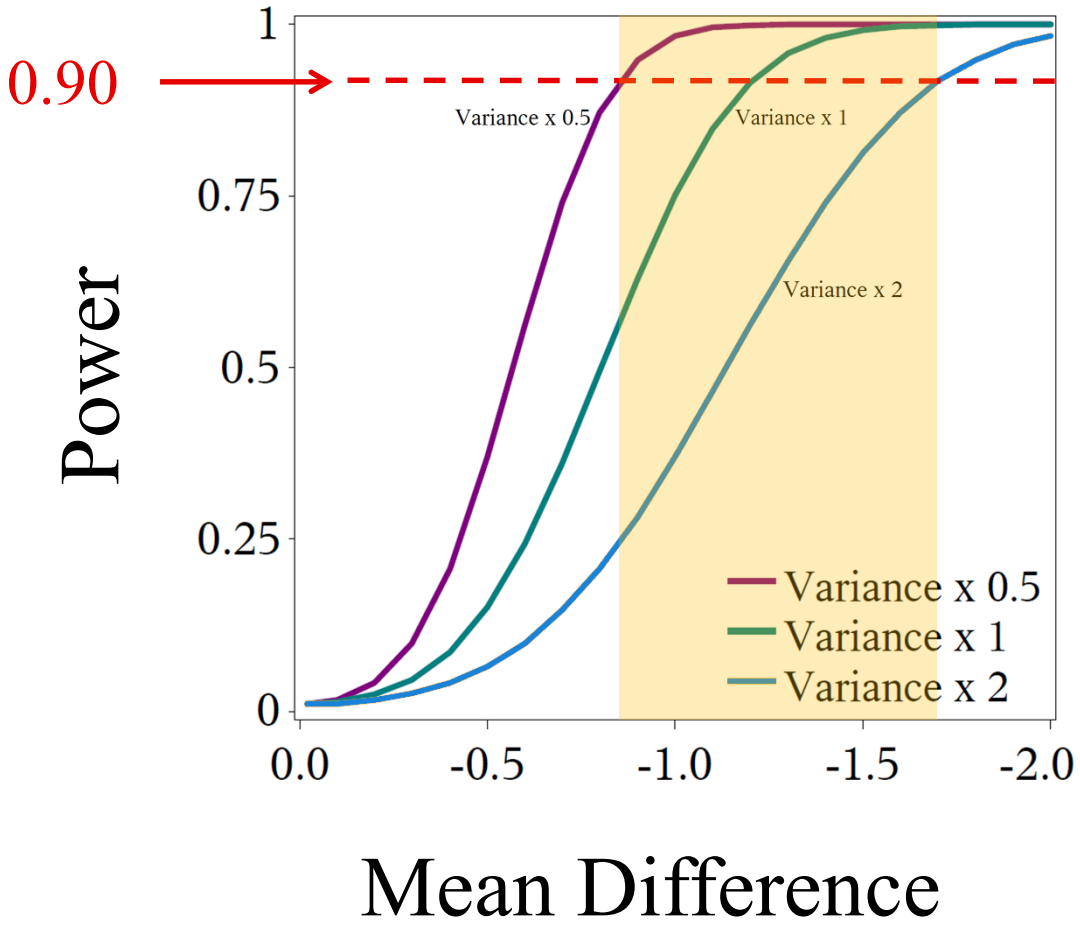
Accounting for Uncertainty



Accounting for Uncertainty



Accounting for Uncertainty



Handling Missing Data

- Assume 25% loss to follow-up.
- Inflate calculated sample size by dividing calculated result:

$$38 \div (1 - 0.25) = 50.7$$

- Round up, to 51, and increase the result to make it divisible by the number of groups, yielding 52.

Sample Size Calculation Summary

Over 12 months, we expect **25% loss to follow up**. We will inflate the sample size to account for the attrition, for a total enrollment goal of **52 participants**, or 26 participants per treatment arm.

The clinic treats **30 patients per week** with the high desire/low felt coping style. Based on recruitment experience for previous studies, we expect a **40% consent rate**. At an effective enrollment of 12 participants per week, we will reach the enrollment goal of **52 participants in 5 weeks time**.

FAIR Training Materials at www.SampleSizeShop.org

- A free short course is available, *Power and Sample Size for Multilevel and Longitudinal Study Designs*.
- The course was designed for scientists, and tested with over 200 scientists and statisticians.
- The material was presented as a two-credit course.
- The course materials (~1,000 slides, home works, answers, screenshots, and video lectures) are individually available at "Sample Size Workshop" menu item on www.samplesizeshop.org.
- Tutorials, applied articles, and theory articles are also linked.

What is Not Available

- GLIMMPSE software covers only a subset of mixed models: incomplete designs are not allowed.
- Continuous predictors are limited to being simple covariates.
- Unequal cluster sizes are not covered.
- Missing repeated measures are not allowed.
- Binary, Poisson and survival outcomes are not allowed.
- High dimensional problems are ignored.
- No power software covers everything.

  There is much room for future methodological research.

  There is much room for extensions to the software.

We Plan to Add What Users Want

- The preferences of users will guide us.
- We are seeking funding to continue the project.

Outline

- An original study is *reproducible* if a new sample of data collected under the original protocol is likely to lead to the same conclusions as the original study.
- To be reproducible, a study must have good statistical power.
- Advances in power theory make it accurate and fast to compute power for linear mixed models.
- Free point-and-click software makes it easy to compute power.
- Planning a longitudinal clinical trial illustrates the process.
- No power software covers everything. There is much room for future methodological research, and extensions to the software.

Questions?

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- Also see www.SampleSizeShop.org