Statistical Design and Power for Proposed Pilot Study 4:
The Care After Life-threatening Events (CALME) Study
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Below we outline the statistical approach we will use to investigate the specific aims and associated hypotheses for this pilot study.

Aim 1: *To test the feasibility of a home-based heart rate variability biofeedback (HRVB) intervention in survivors of cardiac arrest (CA). Specifically, the primary purpose of this pilot study is to assess feasibility, acceptability, appropriateness, usability, and compliance for an at-home, 3-week HRVB intervention in 10 participants.*

Aim 1 will be tested by assessing the following measures:

> *(1) proportion of CA survivors eligible for this pilot study whom we approach and contacted who agree to participate in the trial of HRVB;*
>
> *(2) proportion of participants who complete the outcome assessments at Visit 3;*
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> *(3) proportion of participants that complete a majority (≥ 8 of 15) of the at-home HRVB sessions;*
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> *(4) proportion of participants who report scores ≥ 4 for their final rating of the intervention's feasibility;*
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> *(5) proportion of participants who report scores ≥ 4 for their final rating of the intervention's acceptability;*
>
> *(6) proportion of participants who report scores ≥ 4 for their final rating of the intervention's appropriateness for reducing anxiety;*
>
> *and (7) proportion of participants who report total scores ≥ 68 for their final rating of the intervention's usability.*

Statistical approach for Aim 1. In addition to computing the proportions listed above, we will conduct secondary analyses regarding measures 4, 5, and 6 (see above) as follows. A one-tailed t-test will be conducted comparing the mean for each scale against the comparison value of each 5-point scale's midpoint of 3.

Sample size and power estimates are based on Aim 1. Although some have used pilot studies to estimates effect sizes on primary outcomes, we agree with leaders in our field who argue that effect size estimates from small pilot studies are too imprecise to meaningfully inform effect size assumptions of power analyses for larger, later stage studies. Therefore, we do not provide power calculations for the effects of our intervention on fear-based mechanisms or behavioral outcomes. We will, however, use estimates from these studies (e.g., standard deviations, attrition rates) to help determine appropriate sample sizes for a subsequent study that is powered to detect meaningful reductions in measures of interoceptive bias.

As this is a pilot study, our sample size was guided by the need to enroll enough participants who recently survived CA to examine the feasibility of conducting a larger stage II or III randomized clinical trial of our HRVB intervention in this patient population. In particular, we will determine whether we are capable of recruiting, retaining, and assessing participants as well as implementing the desired intervention with good compliance. If the observed proportion of eligible participants who agree to participate in the trial is 40%, 50%, or 60%, and we therefore have to approach 25, 20, 17 patients, respectively, in order to enroll 10 patients in this pilot. This number is entirely feasible because the large observational trial of CA patients has enrolled 114 participants in a two-year period with eligibility criteria that largely overlap with this pilot study.

Regarding the secondary analyses for Aim 1 for feasibility, acceptability, and appropriateness, we conservatively estimate that we will have sufficient power to detect a significant difference from the three scales midpoints based on the following pilot data. In our pilot study of in-clinic heart rate variability training in patients with acute coronary syndromes, eight patients were asked to indicate to what extent they agreed with the following statement: "Based on my experience today, I believe that this procedure could be helpful for lowering feelings of anxiety." The possible responses were as follows: 1 *Strongly disagree*, 2 *Somewhat disagree*, 3 *Neither agree nor disagree*, 4 *Somewhat agree*, and 5 *Strongly agree*. We observed that a total of

8 participants reported a mean of 4.75 (*SD* = 0.46). In a one-tailed *t*-test with a conservatively high comparison value of 4 (*Somewhat agree*), participants reported significantly *even more* strongly that they believed the HRVB intervention was appropriate for reducing anxiety, $t(7) = 4.58$, $p = .003$, Cohen's $d = 3.05$. This finding indicates that even just 8 participants were sufficient to detect an effect of HRVB on ratings of intervention appropriateness. This assessment is conservative given that the comparison value for the pilot data (4) was above the midpoint, whereas the comparison value for our Hypothesis 1A is the midpoint (3). The pilot data effect was detected with over 90% power, and we will require 80% power for this proposed pilot study. Therefore, we conservatively estimate that 10 participants will be sufficient to detect favorable ratings of intervention appropriateness. Similarly, we extend this rationale to the ratings of intervention feasibility and acceptability as well as usability.

Aim 2: *To assess whether cardiac-related interoceptive fear, anxiety and negative affect decrease from baseline to the 3-week visit and from baseline to the 6-week visit among CA survivors completing the HRVB intervention.*

Aim 2 will be tested by assessing the following measures:

> *(1) Visit-2-to-3 change in cardiac-related interoceptive fear (measured as the within-person difference in the sum of the four cardiac-related items from the physical subscale of the Anxiety Sensitivity Index)*
>
> *(2) Visit-2-to-3 change in trait anxiety (measured as the within-person difference in the total score of the trait version of the State-Trait Anxiety Inventory);*
>
> *and (3) Visit-2-to-3 change in trait negative affect (measured as the within-person difference in the total score of the negative subscale of the Positive and Negative Affect Schedule).*

Statistical approach for Aim 2. We will test this aim by evaluating the change scores listed above. We hypothesize that the pattern of means will reveal a reduction in trait anxiety and negative affect. As mentioned above, this Phase-I trial is not powered to test the significance of these changes, nor is there a control comparison group to test whether the effects are caused by the HRVB intervention in this feasibility pilot study.

Exploratory Aims: *(1) To assess whether HRV increases over the course of the at-home training sessions across participants (measured as the natural log of the root mean square of the successive difference [lnRMSSD]). (2) To assess whether individual differences in the slope of change in HRV over the course of the study is positively associated with the magnitude of reduction in cardiac-related interoceptive fear, trait anxiety, or negative affect.*

Statistical approach for Exploratory Aims. (1) We will use participants' exported and deidentified HRV data to compute lnRMSSD, a standard measure of beat-to-beat HRV. For each participant, we will use a linear regression equation to find the line of best fit that represents the slope of HRV change over time for all available training sessions where time (day since baseline) is the predictor and HRV is the outcome. We will assess what proportion of participants show a positive slope (> 0). (2) We will correlate this slope with the Visit-2-to-3 change in cardiac-related interoceptive fear, the Visit-2-to-3 change in trait anxiety, and the Visit-2-to-3 change in negative affect.

Planned Interim Analyses. Given the relatively small sample size of this study ($N = 10$ participants) and the expected minimal risk of HRVB, interim analyses will not be planned. Nevertheless, if concerns arise related to adverse events, as outlined in the data safety monitoring plan, then an unblinded interim analysis may be conducted, and the trial may be stopped early.