Mindfulness-Oriented Recovery Enhancement for Opioid Misuse and Chronic Pain in Primary Care: A Randomized Controlled Trial

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Title	**Mindfulness-Oriented Recovery Enhancement for Opioid Misuse and Chronic Pain in Primary Care: A Randomized Controlled Trial**
Study Design	The design is a parallel group superiority trial. The unit of randomization is the individual patient.
Study Duration	5 years.
Trial Sites	University of Utah Health – Community Physicians Group.
Objective	Conduct a randomized controlled trial to determine the efficacy of a Mindfulness-Oriented Recovery Enhancement intervention for opioid misuse and chronic pain in primary care.
Number of Subjects	The target sample size is 260 participants enrolled (200 + oversampling by 30% for attrition) to provide 80% probability that a two-sided 95% confidence interval will have a margin (half-width) less than +/- .18 standard deviation for the between-groups difference in the study outcomes.
Main Inclusion Criteria	Age ≥18 with a chronic pain-related diagnosis, reporting current pain ≥3 on a 0-10 scale, currently taking prescription opioids for ≥3 months, and surpassed a validated cutpoint for opioid misuse on the Current Opioid Misuse Measure (COMM).
Intervention	Mindfulness-Oriented Recovery Enhancement (MORE) is a group behavioral intervention that unites mindfulness training, cognitive reappraisal, and positive psychological principles into an integrative intervention strategy targeting mechanisms of pain and opioid misuse.
Duration of Intervention	8 weeks.
Primary Outcome	The primary outcome is opioid misuse measured by the Drug Misuse Index, operationalized as scores on the COMM and triangulated by blinded clinical interview and urine drug screen. The co-primary outcome is chronic pain symptomology, operationalized as pain severity and functional interference scores on the Brief Pain Inventory (BPI).

Primary Analysis	Effects of treatment on the DMI will be analyzed with generalized mixed effects models, and effects on the BPI will be analyzed with mixed effect ANCOVA models, adjusting for baseline levels.
Secondary Outcomes	Opioid dose, psychological distress, and opioid craving.
Interim Analysis	Interim monitoring will focus on patient accrual, baseline comparability of treatment groups, protocol adherence, data completeness and quality, and safety. No interim outcome analysis is planned.

1. BACKGROUND

Prescription opioid misuse among chronic pain patients is an emerging public health threat that is being addressed with heightened urgency at both clinical and policy levels. Though opioid analgesic therapy can manage chronic pain, it may confer with significant health risks, including dependence, overdose, and misuse. Opioid misuse is evidenced by aberrant drug-related behaviors such as unauthorized dose escalation or use of prescribed opioids to self-medicate negative emotions that exacerbate craving.[6] Research on treatments for opioid misuse among chronic pain patients is scant; according to a 2015 NIH-AHRQ systematic review of long-term opioid therapy for chronic pain, "no study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse."[7] Extant therapies may have limited efficacy because they fail to directly target cognitive-affective neural circuits that govern hedonic regulatory responses elicited by pain-, opioid-, and reward-related stimuli.[8] To address this need, the PI translated mechanistic findings from behavioral neuroscience into an innovative treatment for prescription opioid misuse, called **Mindfulness-Oriented Recovery Enhancement** (MORE). MORE integrates training in mindfulness, reappraisal, and savoring of natural rewards to enhance hedonic regulation and target the risk chain at the point where maladaptive emotion-cognition interactions link chronic pain to opioid misuse. MORE is innovative in that it aims to modify associative learning mechanisms dysregulated by the allostatic effects of opioid misuse on brain reward systems via strengthening **top-down cognitive control to restructure bottom-up reward learning from valuation of drug reward to natural reward** – something that no other behavioral intervention for opioid misuse has been designed to do. Accordingly, this project funded by the National Institute on Drug Abuse (NIDA) is a randomized clinical trial (RCT) of MORE to reduce opioid misuse and chronic pain symptoms among patients receiving long-term opioid therapy in primary care.

2. AIMS

AIM 1. To conduct a RCT of the Mindfulness-Oriented Recovery Enhancement (MORE) intervention for co-occurring aberrant drug-related behaviors and chronic pain in primary care.
We will compare the therapeutic impact of MORE and a conventional supportive group (SG) psychotherapy active control condition on clinical outcomes germane to opioid misuse and chronic pain. **Hypotheses**: Opioid misusing patients assigned to MORE, as compared to SG participants, will evidence decreased opioid misuse and pain (*PRIMARY OUTCOMES*), as well as reduced opioid craving, opioid dosing, and psychological distress (*SECONDARY OUTCOMES*) from pre- to post-treatment through 9-month follow-up.

AIM 2. To test and quantify the degree to which MORE's impact on opioid misuse and pain is mediated by proactive control over emotion-cognition interactions (top-down mechanism).
Hypotheses: The impact of MORE on opioid misuse and pain will be mediated by improvements in: **a)** attentional disengagement from opioid-related cues (reduced attentional bias); **b)** emotion regulation**;** and **c)** cognitive coping (e.g., reinterpretation of pain as innocuous sensory information).

AIM 3. To test and quantify the degree to which MORE's impact on aberrant drug-related behaviors is mediated by restructuring of reward processing (bottom-up mechanism).

Hypotheses: The impact of MORE on aberrant drug-related behaviors will be mediated by restructured reward processing, as indicated by **a)** decreases in psychophysiological indices of opioid cue-reactivity; **b)** increases in responsiveness to natural reward cues; and **c)** a shift in the relative salience of these cues.

3. STUDY DESIGN

A two-arm parallel RCT design with an active control group will minimize internal threats to validity. Mindfulness-Oriented Recovery Enhancement (MORE; n=130) and the Supportive Group Psychotherapy control (SG; n=130) will be equated for time spent in treatment. Assessors will be blind to treatment condition. Target sample sizes were determined via power and precision analyses. The unit of randomization is the individual patient. The co-primary outcomes are opioid misuse and chronic pain symptoms. Participants will complete a clinical assessment battery at pre- and post-treatment, and at 3-, 6-, and 9-month follow-ups. Participants will complete a psychophysiological assessment protocol at pre- and post-treatment. Participants will complete ecological momentary assessments (EMAs) of symptoms, skill practice, and opioid use during treatment and 1 month afterward up to 3 times/day (morning, noon, and night).

4. ENDPOINTS

The primary, secondary, and tertiary outcome measures are summarized in Table 1.

Event	Screen	Pre -Tx	In Tx	Post-Tx	Follow-Up			
					1 Mo	3 Mo	6 Mo	9 Mo
Screening and Stratification Measures								
Informed Consent	X							
Demographics & Medical History	X							
MINI	X							
Primary and Secondary Outcome Measures								
BPI Pain severity and interference		X		X		X	X	X
DMI: ABC, COMM & Urine screen		X		X		X	X	X
Opioid dosing – TLFB and chart review		X		X		X	X	X
DASS Psychological distress		X		X		X	X	X
Opioid Craving NRS – EMA (see below)			X			X		
Mediators								
Self-report mediators: CSQ Reinterpretation FFMQ Mindfulness CERQ Reappraisal WOS Savoring		X		X		X	X	X
Other tertiary measures: PANAS Affect CSQ Pain Catastrophizing MLQ Meaning in Life SHAPS Anhedonia PCL PTSD Self-Transcendence		X		X		X	X	X
Psychophysiological protocol		X		X				

Intervention Process Measures and Ecological Momentary Assessments								
TMS State mindfulness (after each session)			X					
Opioid craving NRS - EMA			X			X		
Opioid dosing – EMA			X			X		
Affect NRS - EMA			X			X		
Pain Intensity & Unpleasantness NRS - EMA			X			X		
Therapeutic skill practice			X			X		

4.1 Primary Outcomes

The primary outcome is opioid misuse measured by the Drug Misuse Index, operationalized as scores on the COMM and triangulated by blinded clinical interview and urine drug screen. The co-primary outcome is chronic pain symptomology, operationalized as pain severity and functional interference scores on the Brief Pain Inventory (BPI). Overall success of the intervention will occur if opioid misuse decreases and pain functioning improves, while pain severity does not worsen. For conservatism, we evaluate all outcomes with two-sided tests, and the Bonferroni correction to control for multiple comparisons.

Primary outcomes (PRE/POST/FOLLOW-UP). Our pre-specified primary **opioid misuse** outcome in clinicaltrials.gov is a validated composite measure - the Drug Misuse Index (DMI).[11] Because there is no single way to identify patients who misuse opioids,[12] the DMI uses 3 levels of data to triangulate opioid misuse: self-reports on a structured questionnaire (i.e., the COMM); clinical assessment of opioid misuse—the Addiction Behaviors Checklist (ABC)[13]—rated by clinical staff (i.e., psychologists, social workers, and nurses) blinded to treatment assignment; and urine toxicology screens. The COMM consists of 17 items rated on a Likert scale (0=never, 4=very often) regarding how often in the past 30 days patients engaged in opioid misuse-related behaviors (e.g., used opioids in ways other than prescribed). COMM scores ≥9 and ABC scores ≥2 are considered positive. A positive rating from the urine screen is given when subjects test positive for illicit drugs or a non-prescribed opioid. Subjects with positive COMM scores will be given a positive DMI and classified as a misuser. If patients deny engaging in opioid misuse-related behavior (COMM scores <9), then positive ratings on both the urine screen and the ABC are needed for a positive DMI, because urine screens can be inaccurate due to variable drug metabolites, and clinician ratings may unreliable.[14,15] Otherwise, subjects will be given a negative DMI. Multiple studies support the validity of this DMI scoring method.[11,16–18] **Chronic pain symptoms** (pain severity and functional interference) will be assessed with the Brief Pain Inventory (BPI).[19]

4.2 Secondary Outcomes

Opioid craving will be measured with 2 items “How much do you want to take your opioids right now?” and “How strong of an urge do have to take opioids right now?” using 0-10 Numeric Rating Scales (NRS) delivered via EMA. Single item measures of craving have been shown to validly predict opioid misuse[16] and be sensitive to MORE treatment effects.[3] **Reduction in opioid dose** will be assessed by the Timeline Followback Procedure (TLFB) and triangulated by chart review of prescription history by the study coordinator.[20] Opioid dose will be converted to oral morphine-equivalent using standardized equianalgesic conversions. Subjects will also document daily opioid dose via EMA. **Psychological distress** will be measured with the Depression Anxiety Stress Scale-21 (DASS-21), a validated, reliable scale (α=.87-.94).[21]

4.3 Tertiary Outcomes

The tertiary outcomes include psychophysiological measures, self-report mediators, and other EMA ratings of momentary affective state and momentary pain ratings.

5. RANDOMIZATION

5.1 Method of Randomization

An electronic random number generator will randomize participants with simple random assignment in blocks of varying sizes (2 - 4) to preserve unpredictability of allocation, which will be concealed by opaque envelopes.

All participants who met trial eligibility criteria were randomized via simple random assignment.
A computerized random number generator produced the simple random assignment. An investigator uninvolved in recruitment, consenting, assessment, or follow-up generated the assignment. No one else from the trial was involved in the process. To minimize the risk of selection bias, the investigator who generated assignments had no contact with or knowledge of study participants at the time of random assignment.

5.2 Allocation Concealment

Allocation concealment is an important consideration for randomized trials to control for selection bias. To prevent bias and maintain allocation concealment, participants will not be allocated until the day of the first treatment session. Assessments will be conducted by project staff blinded to group assignment (which remained concealed throughout the study). To maintain blinding, the allocation list was inaccessible to project staff involved in assessment or treatment, and before each assessment, participants were reminded to not reveal anything that would disclose their treatment assignment to study staff.

6. SAMPLE SIZE

6.1 Preliminary Data

Sample size considerations are based the effects of MORE versus SG on opioid- and pain-related variables from the PI's NIDA R03 grant (R03DA032517). The PI's R03-funded Stage 2 RCT identified medium to large effect sizes on pain and opioid-related variables over the course of the study (Cohen's *d*=.50 - .84).

6.2 Sample Size Determination

The table indicates the smallest detectable effects for a treatment X time interaction term given different sample sizes, assuming a Type I error rate of .05 and varying correlations between repeated measures, which ranged from .34 -.56 per outcome in the R03. Cohen[26] defined *f*=0.10 and *f*=0.25 as small and medium effects, respectively. Thus our target N of 260 (N=200 + oversampling by 30% for attrition) will allow us to detect small-to-medium effects on continuous outcomes. Based on dichotomous clinical classification of opioid misuse data from the R03 (68% improvement for MORE versus 32% for SG), the proposed sample size will offer outstanding power (>.99) to detect differences of this magnitude on this outcome. (b) *Precision of parameter estimation*. Our target N will allow model parameters to be estimated with a high degree of precision. A per group sample size of N=130 provides 80% probability that a two-sided 95% confidence interval will have a margin (half-width) less than +/- .18 standard deviation. Thus the proposed sample will provide precision more than adequate for estimating small clinical effects with high confidence. (c) *Multivariate models*. Generally, structural equation power calculations for the full information maximum likelihood sensitivity analyses can be based on Root Mean Square Error of Approximation (RMSEA) comparisons of nested models. The proposed sample provides, in a realistic testing scenario, greater than 80% power in a 1 *df* test (26 versus 25) of close fit comparing two models with RMSEA of .06 and .05 at α=.05. These calculations are conservative. Maximum likelihood techniques retain all observations at all times, and efficiently incorporate correlated observations to yield an Effective Sample Size that is quantifiably larger than the number of subjects. With fully specified repeated dimensions, the anticipated correlations will yield an effective sample size that is 40% larger, or roughly N=360.

Table 2. Sample Size Estimates

Minimally detectable effect sizes (Cohen's *f*) for treatment X time interaction (pre-tx, post-tx, follow-up)				
Correlation	N = 100	N = 110	N = 120	N = 130
0.25	0.16	0.15	0.14	0.14
0.50	0.13	0.12	0.12	0.11
0.75	0.09	0.09	0.08	0.08

Due to COVID-19 and related research restrictions at the University of Utah, recruitment ended on March 31, 2020, with a total of 250 participants enrolled (10 participants less than the originally anticipated target N).

7. INTERIM MONITORING PLAN

7.1 Overview

Interim monitoring will focus on patient accrual, baseline comparability of treatment groups in terms of demographic and clinical characteristics, protocol adherence, loss to follow-up, data completeness and quality, and safety.

7.2 Monitoring of Safety

Details of the safety and adverse event monitoring plan were provided in the study protocol. This is a minimal risk trial. Adverse and serious adverse events will be collected. Unanticipated problems will also be reported to the Medical Safety Monitor.

8. ANALYTIC PLAN

8.1 Overview

The analysis of the primary and secondary outcomes will be according to the principle of intent-to-treat, i.e., participants will be analyzed according to their original treatment assignment regardless of adherence to protocol. SAS 9.4, MPlus, and R 3.0.2 software will be used for all analyses.

8.2 Comparability of Treatment Groups

Comparability of treatment groups will be assessed by comparing the distribution of baseline characteristics in the two groups using appropriate graphical procedures, summary statistics and multivariate methods. The randomization is designed to produce balance on important covariates and baseline levels of the outcome measures. Nonetheless, some degree of pre-randomization imbalance in study outcomes may occur, and we regress post-randomization observations on baseline scores to adjust for such imbalance.

8.3 Analysis of the Primary Outcomes

Effects of treatment on opioid misuse and chronic pain symptoms will be evaluated using linear and nonlinear mixed models with fixed effects consisting of a time factor and between-subjects treatment factor (MORE vs. SG), and will adjust for randomization imbalance by covarying baseline levels of the outcome. For the continuous pain symptom outcome measured by the

Brief Pain Inventory (BPI), the longitudinal trajectory for individual *i* on outcome *j* in treatment group *g* at post-randomization time *t* is modeled, under the full-rank parameterization, as

(1) $y_{ijg,t>1} = a_{ijg} + \beta y_{ijg,t=1} + \mu_{jg,t>1} + \varepsilon_{ijg,t>1}$, $a_{ijg} \sim N(0,\psi_j)$, $\varepsilon_{ijg,t>1} \sim MVN(0,\Theta_j)$,

where

a_{ijg} is a random intercept with zero mean and variance ψ_j,

β is the fixed regression coefficient of the post measures on pre-randomization baseline (time 1) score $y_{ijg,t}$=1

$\mu_{jg,t>1}$ are the post-randomization treatment arm means at times 2 through 5, conditioned on baseline, equivalent in this parameterization to distinct intercept terms $\mu_{jgt>1} = E(y_{ijg,t>1} \mid a_i, y_{ijg,t=1})$ for each group and time, and $\varepsilon_{ijg,t>1}$ are multivariate normal random error terms assumed to follow either an independent scaled diagonal or AR1 error structure, as determined by comparison of BIC model statistics.

Opioid misuse as measured by the Drug Misuse Index (DMI) is a dichotomous longitudinal variable Y, and we will evaluate treatment impact with a generalized linear mixed model specifying a binary distribution and logit link, with time *t* and group *g* as categorical factors and a random intercept ζ_i :

$$\log(\pi_i / (1-\pi_i)) = \alpha_g + \beta_t + \gamma_{gt} + \zeta_i$$

$$Y_{igt} \mid \zeta_i \sim Bernoulli(\pi_{igt}),\ \zeta_i \sim iid\ N(0,\psi)$$

.

For the opioid misuse outcome (Drug Misuse Index; DMI), it is not necessary to adjust for baseline differences, as all participants exhibited opioid misuse at baseline.

Our primary interest lies in estimating, for the BPI co-primary pain outcome j, the adjusted main effect, which represents the overall benefit of treatment across all four post-treatment measurement points conditional on baseline:

(2) $\hat{\delta}_j = (1/4)\sum_{t=2}^{t=5} \hat{\mu}_{g=SG,t} - \hat{\mu}_{g=MORE,t}$, a linear combination over the four post-randomization (t>1) adjusted treatment means. The key estimand for binary DMI will be the main effect on the additive logit scale over the four post-randomization occasions.

This estimand is meaningful whether a time-by-treatment arm interaction is present or not, as it represents the expected overall treatment benefit for individuals randomly selected from the two populations. The null hypothesis of no treatment impact is $H_{0j} : \delta_j = 0$, a single numerator degree-of-freedom test, which we evaluate at alpha=.05/3 = .0167 (i.e., Bonferroni adjustment for the three primary variables) under restricted maximum likelihood with Kenward-Roger denominator degrees of freedom. To control for false discovery in the three primary outcomes, we will compare the unadjusted p-values against Bonferroni-adjusted alpha =.05/3 = .0167.

The analysis of primary outcomes achieves unbiased estimates of model parameters when missingness arises from processes that depend on observed covariates (Missing at Random, or MAR). Maximum likelihood estimation (MLE) procedures under an intent-to-treat philosophy are robust against common patterns of missing data.[27,33] MLE is based on all data observations; no values are deleted or imputed. In our tables and reporting, we refer to the p-values under the standard MAR assumption as p_{MAR}. There is however no definitive test for the MAR assumption. But we investigate sensitivity to missing data and possible other covariates using two other approaches. We extend the scope of the MAR analysis using Full Information (Direct) Maximum Likelihood under broader multivariate patterns of missingness, incorporating simultaneous longitudinal outcomes and key sociodemographic variables as auxiliary variables correlated with the outcome. In simulations, this approach often yields performance equal to or better than achieved by multiple imputation and explicit nonignorable missingness models.[34–36] These analyses will be conducted with the latent variable modeling program MPlus, which

incorporates full information maximum likelihood estimation in multivariate models. The global hypothesis test will be examined under three sensitivity variations:

a) Replication of the analysis model (1) under simultaneous inclusion of the three primary outcomes of drug misuse, pain severity, and pain interference, repeated over post-randomization assessments, along with respective baseline predictor values. In this multivariate analysis, pain severity and pain interference are continuous variables, while drug misuse is represented as a dichotomous outcome under a logit link. All three outcomes are free to correlate in the analysis, with the global hypothesis test imposed by nonlinear equality constraints on the net benefits $H_{0j}: \delta_j = 0$ for j=1,2,3, a 3 df test.

b) Replication of the 3 df global hypothesis test in (a) with the addition of the continuous log-transformed opioid use secondary outcome, and the continuous Distress secondary outcome as correlated variables.

c) Replication of (b) with the addition of the demographic predictor variables gender and continuous age at baseline.

(d-f) Re-running variations a, b, and c under constrained longitudinal analysis (CLDA) rather than regression adjustment for baseline. Under CLDA, the baseline means are constrained to be equal across arms. These constraints are straightforward under multivariate modeling. The overall benefit contrasts among the post-baseline means, conditional on within-outcome baseline treatment arm equalities, are equivalent to the difference in areas under the curve for the conditional post-baseline mean trajectories.

In the text and tables, we report p-values obtained under Model C as p_{MAR+}, to indicate that the standard MAR analysis has been supplemented with several auxiliary variables, as described above.

Finally, we re-estimated all analyses under a simple selection model[37,38] in which missingness is dependent on the value of the unobserved outcome in as well as the prior observed responses. In the text and table, we report p-values obtained under this model as p_{NMAR}. The Not Missing at Random designation indicates that this model does not require the more restrictive assumptions of MAR, but may be valid when missingness depends on underlying and unobserved values.

8.4 Analysis of the Secondary and Tertiary Outcomes.

Analysis of opioid medication dose will also be implemented as a linear mixed effects model of longitudinal morphine equivalent intake, conditional on baseline, under a log transformation to reduce skew. Distress and other psychological outcomes will similarly be analyzed using linear mixed models adjusted for randomization imbalance by covarying baseline levels of the outcome. Exact unadjusted p-values are reported for the secondary and tertiary outcomes. As in the analysis of our continuous primary outcomes, our primary interest lies in the adjusted main effect of treatment, which with this model specification represents the average effect of treatment across all post-treatment measurement points.

Control for multiple comparisons among the secondary and tertiary variables is provided by a global hypothesis test evaluated at alpha=.05 in the multivariate mixed effects model as $H_{0,\text{joint}}: \forall j, \delta_j = 0$ versus $H_{1,\text{joint}}: some\ \delta_j \neq 0$ for some *j*. Multivariate contrasts may be

implemented in the univariate mixed model framework of SAS 9.4 by introducing a categorical indicator variable for outcome *j*, interacting this variable with all other effects, and specifying distinct covariance matrices for each *j*. The global net benefit hypothesis is a custom contrast with *J* df, where J is the number of non-primary outcomes. Rejection of the global hypothesis test implies a significant treatment impact on at least one secondary outcome *j*, and we report exact p-values for the univariate tests.

Descriptive analysis of opioid dosing data will examine group differences in the proportion of participants who achieve an opioid dose reduction of ≥50% at each time point.

To explore whether the cognitive, affective, and physiological mediators specified in **Aims 2 and 3** statistically mediate the effect of treatment on outcome variables, we will conduct structural equation path analyses according to established guidelines[28] by evaluating three regression paths: A) *'a'* path between treatment indicator and change in outcome (e.g., opioid misuse) from pre-treatment to follow-up; B) the *'b'* path between pre-post treatment change in the mediator (e.g., attentional bias) and pre-treatment to follow-up change in the outcome (e.g., opioid misuse); and C) the *'c'* path between treatment and pre-post treatment change in the mediator (e.g., attentional bias). We will test mediation by evaluating the significance of the joint product of the *a* and *b* paths, with bootstrapping[29] used to test the significance of the indirect effect. Our team developed a comprehensive analysis of mediation under possible moderation for clinical trials,[30] allowing for the possibility that treatment has changed relationships, not just levels, among variables - this will further guide analyses for Aims 2 and 3. Path models will be corrected for multiple comparisons. Mediational analyses will be published in a subsequent report following publication of the primary trial outcomes.

For EMA, we will use growth curve analysis[31] to examine treatment and homework practice effects on: trajectories of craving (and other tertiary EMA outcomes – e.g., affective state). The basic growth curve model will be specified with fixed effects consisting of continuous time *t* (in days), categorical period *p* (AM, Noon, or PM reporting) and the categorical between-subjects treatment factor (*g* = MORE vs. SG). Random effects will incorporate correlated intercept and period-specific trend components, as in standard growth models:

$$y_{itpg} = b_{0i} + b_{1ipg}t + \varepsilon_{itpg} \;;\; b_{0i}, b_{1ipg} \sim MVN([\beta_{0p}, \beta_{1pg}]', \mathbf{\Psi}) \,,\, \varepsilon_{itpg} \sim N(0, \sigma^2) \,.$$

The model allows different trends in the three different reporting periods of the day. The key null hypothesis of treatment impact in EMA will be evaluated by testing the equality of the three fixed effect period trends between arms:

$$H_0 : \sum\nolimits_p \beta_{1p,g=SG} / 3 = \sum\nolimits_p \beta_{1p,g=MORE} / 3 = \sum\nolimits_p \beta_{1p} / 3$$

Additional temporal complexity and serial dependence will be considered in polynomial and autoregressive models, as evaluated with the Bayesian Information Criterion. More complicated relationships will be considered in ALT models that include additional cross-lagged and auto-regressive effects.