EAM2025

XI Conference

23RD - 25TH JULY 2025

Spain Tenerife
Canary Islands

European Association of Methodology

Multiphase Optimization Strategy (MOST) for Equitable Cluster Randomized Interventions: Design Considerations and Statistical Modeling

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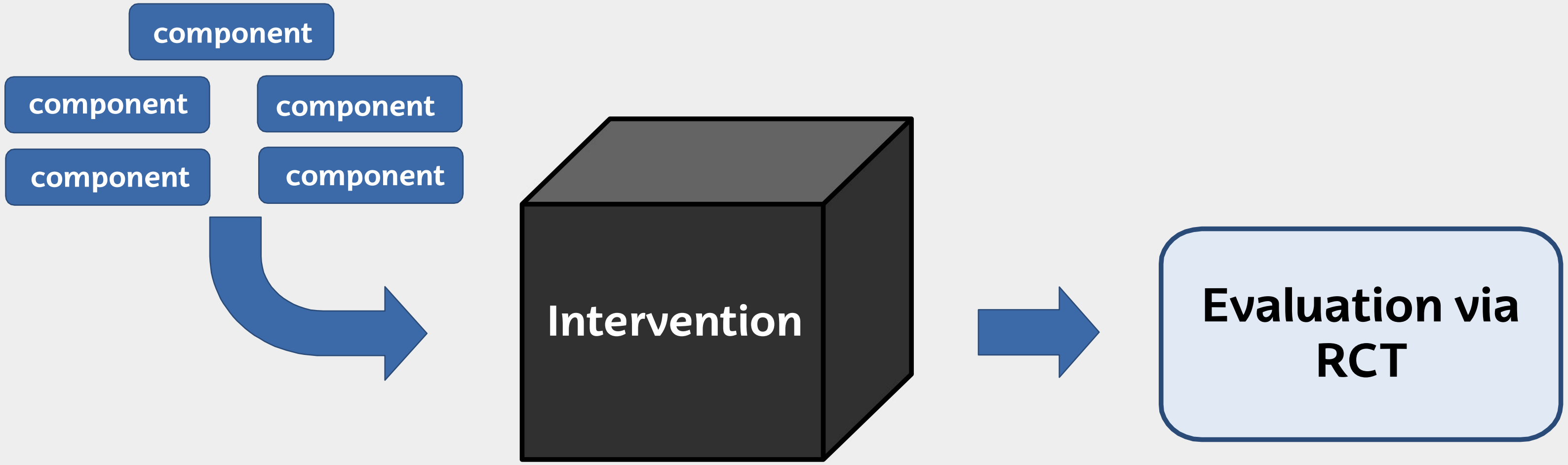
1. Introduction to multicomponent interventions evaluation

Multicomponent interventions are common in the social and health sciences. They are integrated by strategies that operate independently or synergistically to achieve a common objective.

The ***classical evaluation approach*** combines the components into a single package, which is assessed using a randomized controlled trial (RCT).



1. Introduction to multicomponent interventions evaluation

Given these limitations, MOST (*Multiphase Optimization Strategy*) has emerged (Collins, 2018).

This approach enables the optimization of interventions to enhance their effectiveness, efficiency, scalability, and affordability.

MOST enables researchers to identify:

- **Which** intervention components are effective
- **Why** they work (mechanisms of action)
- **For whom** they are most beneficial (moderators of effect)
- **Under what conditions** they produce optimal outcomes (contextual factors)

Collins, L. M. (2018). *Optimization of Behavioral, Biobehavioral, and Biomedical Interventions. Statistics for Social and Behavioral Sciences*. Springer International Publishing. https://doi.org/10.1007/978-3-319-72206-1_1

1. Introduction to multicomponent interventions evaluation

Intervention optimization

Process of identifying an intervention that provides the best expected outcome obtainable within key constraints imposed by the need for efficiency, economy, and/or scalability (Collins, 2018; p. 12).

Effectiveness

Affordability
Scalability
Efficiency

Intervention *EASE*

Collins, L. M. (2018). *Optimization of Behavioral, Biobehavioral, and Biomedical Interventions. Statistics for Social and Behavioral Sciences*. Springer International Publishing. https://doi.org/10.1007/978-3-319-72206-1_1

1. Introduction to multicomponent interventions evaluation

MOST aims to achieve a strategic balance among the properties:

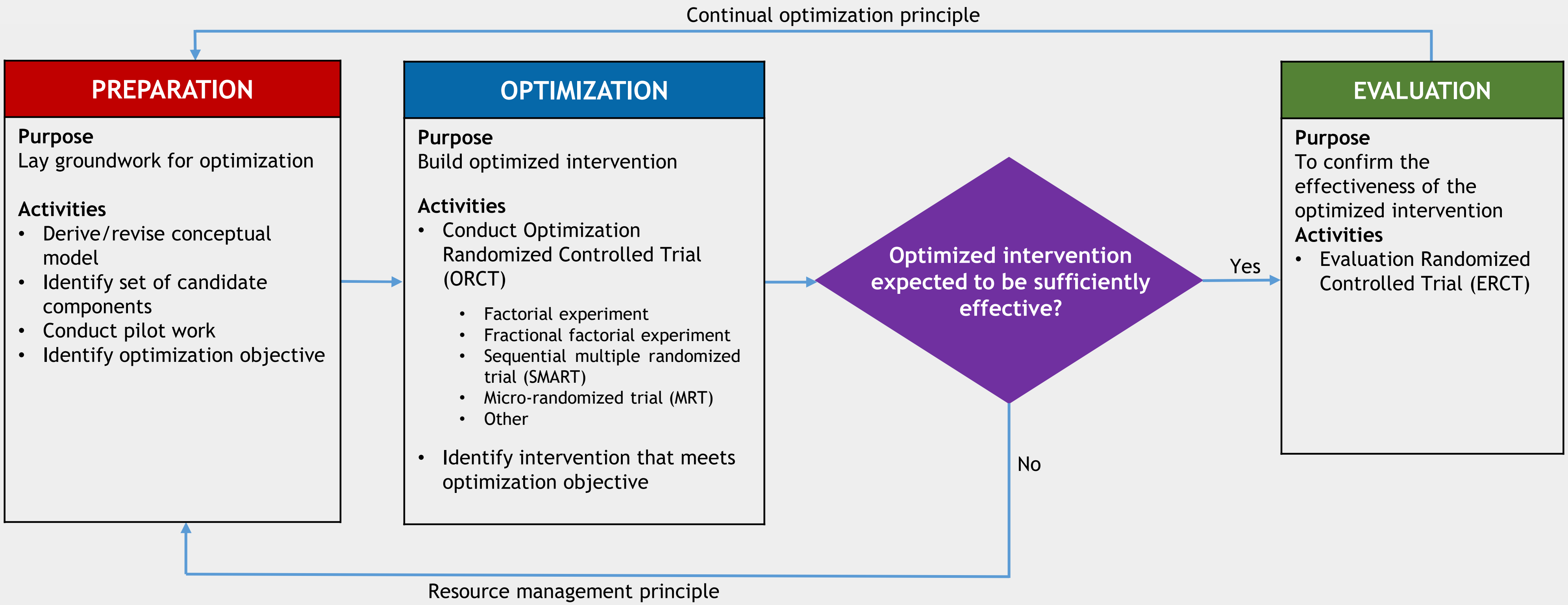
Effectiveness: degree to which the intervention or component produces an outcome in the desired direction.

Affordability: extent to which the intervention is delivered within budget and offers a good value.

Scalability: extent to which the intervention can be implemented in the intended setting without the need for ad hoc modifications.

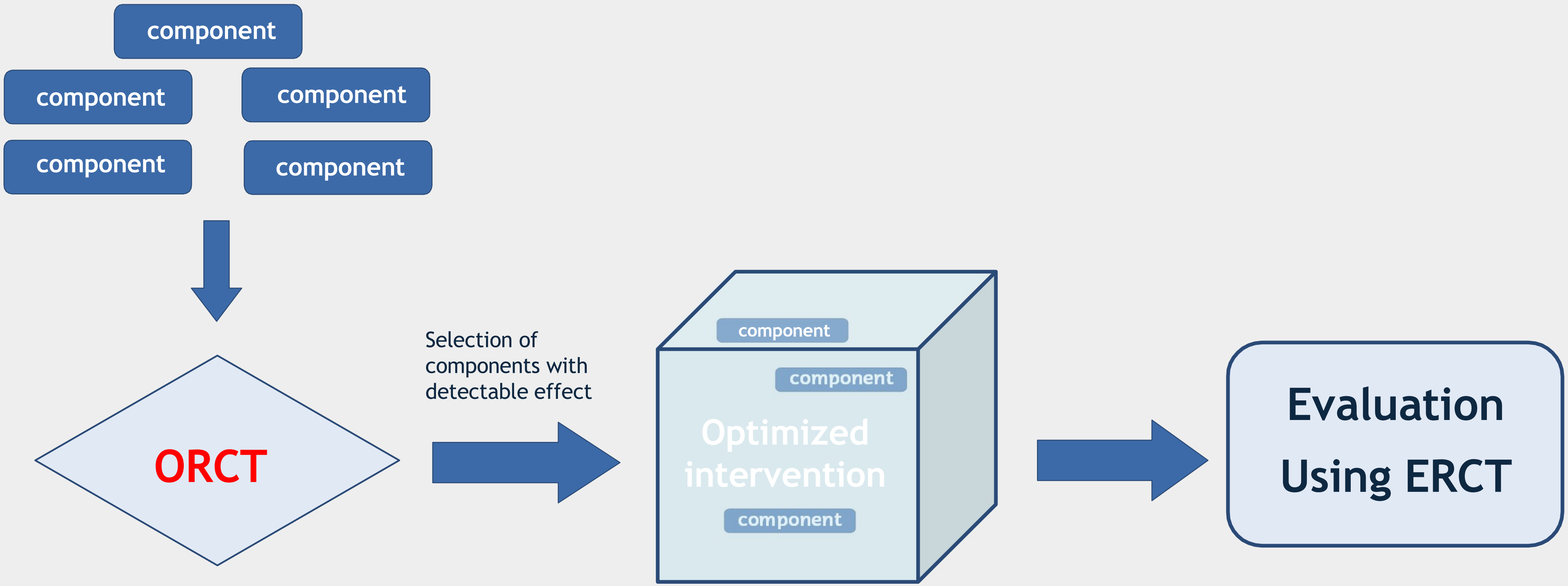
Efficiency: extent to which the intervention is made up solely of active components that, improve outcomes without wasting resources.

1. Introduction to multicomponent interventions evaluation



Adapted from Collins, L. M. (2018). Conceptual introduction to the multiphase optimization strategy (MOST). In L. M. Collins (Ed.), *Optimization of Behavioral, Biobehavioral, and Biomedical Interventions. Statistics for Social and Behavioral Sciences* (pp. 1-34). Springer International Publishing. https://doi.org/10.1007/978-3-319-72206-1_1

1. Introduction to multicomponent interventions evaluation



2. Factorial designs for optimization randomized controlled trials

- 2^k factorial experiment

  Example 2^2: 2x2

- Each factor estimates the performance of a component.

- Factorial ANOVA: estimation of main effects and interactions.

- Factorial designs for ORCTs (optimization randomized controlled trials) could have ≥ 2 levels per factor.

	Component A	
Component B	On	Off
On	A, B on	A off, B on
Off	A on, B off	A, B off

2. Factorial designs for optimization randomized controlled trials

Example of a hypothetical intervention with four components aimed to HIV viral load suppression.

Factorial design 2^4:

- Individual counseling; *IN* (Off [no included], On [included]).
- Peer mentoring; *PM* (Off, On)
- Support groups; *SG* (Off, On)
- Patient navigation; *NA* (Off, On)

Condition number	IN	PE	SG	NA
1	On	On	On	On
2	On	On	On	Off
3	On	On	Off	On
4	On	On	Off	Off
5	On	Off	On	On
6	On	Off	On	Off
7	On	Off	Off	On
8	On	Off	Off	Off
9	Off	On	On	On
10	Off	On	On	Off
11	Off	On	Off	On
12	Off	On	Off	Off
13	Off	Off	On	On
14	Off	Off	On	Off
15	Off	Off	Off	On
16	Off	Off	Off	Off

2. Factorial designs for optimization randomized controlled trials

For α = .05; power = .8; *d* =.3, *N* = 352

Main effect IN:

Estimation: IN main effect= $(\hat{Y}_1+\hat{Y}_2+\hat{Y}_3+\hat{Y}_4+\hat{Y}_5+\hat{Y}_6+\hat{Y}_7+\hat{Y}_8) - (\hat{Y}_9+\hat{Y}_{10}+\hat{Y}_{11}+\hat{Y}_{12}+\hat{Y}_{13}+\hat{Y}_{14}+\hat{Y}_{15}+\hat{Y}_{16})$

Interpretation: effect of IN averaged over the levels of the other three factors.

Condition number	IN	PE	SG	NA	$\hat{Y}$ value	N
1	On	On	On	On	$\hat{Y}_1$	22
2	On	On	On	Off	$\hat{Y}_2$	22
3	On	On	Off	On	$\hat{Y}_3$	22
4	On	On	Off	Off	$\hat{Y}_4$	22
5	On	Off	On	On	$\hat{Y}_5$	22
6	On	Off	On	Off	$\hat{Y}_6$	22
7	On	Off	Off	On	$\hat{Y}_7$	22
8	On	Off	Off	Off	$\hat{Y}_8$	22
9	Off	On	On	On	$\hat{Y}_9$	22
10	Off	On	On	Off	$\hat{Y}_{10}$	22
11	Off	On	Off	On	$\hat{Y}_{11}$	22
12	Off	On	Off	Off	$\hat{Y}_{12}$	22
13	Off	Off	On	On	$\hat{Y}_{13}$	22
14	Off	Off	On	Off	$\hat{Y}_{14}$	22
15	Off	Off	Off	On	$\hat{Y}_{15}$	22
16	Off	Off	Off	Off	$\hat{Y}_{16}$	22

2. Factorial designs for optimization randomized controlled trials

Compared to other types of designs, 2^k factorial designs offer a highly efficient alternative to develop ORCTs.

Designs for example k = 4	Experimental conditions number	Sample size (Power = 0,8; *d* = 0,3)	Interactions estimation possibility
Individual experiments	8	1.408	No
Comparative treatment	5	880	No
Full factorial	16	352	Yes, all

3. Application in HIV prevention study

Implementing factorial experiments in health interventions requires consideration of clustered structures.

In this context we focus exclusively on multilevel factorial designs with randomization at the level of pre-existing clusters.

This approach is exemplified in the optimization of a **primary HIV prevention for patients with opioid use disorder** (Mistler et al., 2023).

"Optimizing evidence-based HIV prevention targeting people who inject drugs on PrEP"

Funded by National Institutes of Health (NIH). Reference: [5R01DA055534-03]; PI: Michael Copenhaver & Tania B. Huedo Medina; Receiving organization: University of Connecticut

Mistler, C. B., Shrestha, R., Gunstad, J., Collins, L., Madden, L., Huedo-Medina, T., Sibilio, B., Copenhaver, N. M. & Copenhaver, M. (2023). Application of the multiphase optimisation strategy (MOST) to optimise HIV prevention targeting people on medication for opioid use disorder (MOUD) who have cognitive dysfunction: protocol for a MOST study. *BMJ open*, *13*(6), e071688. https://doi.org/10.1136/bmjopen-2023-071688

3. Application in HIV prevention study

HIV infection rates among people who inject drugs (PWID) and suffer opioid use disorder has remained largely for the last 15 years in USA (Parker et al., 2019).

Intervention for **primary HIV prevention among patients with opioid use disorder**:

-IMB (Information-Motivation-Behavior Skills) model (Fisher & Fisher, 1992; Huedo-Medina et al., 2016).

-Objective: to optimize a behavioral intervention by identifying which combination of compensatory cognitive strategies (attention, executive functions, memory, and information processing) yields the greatest improvement in HIV prevention outcomes.

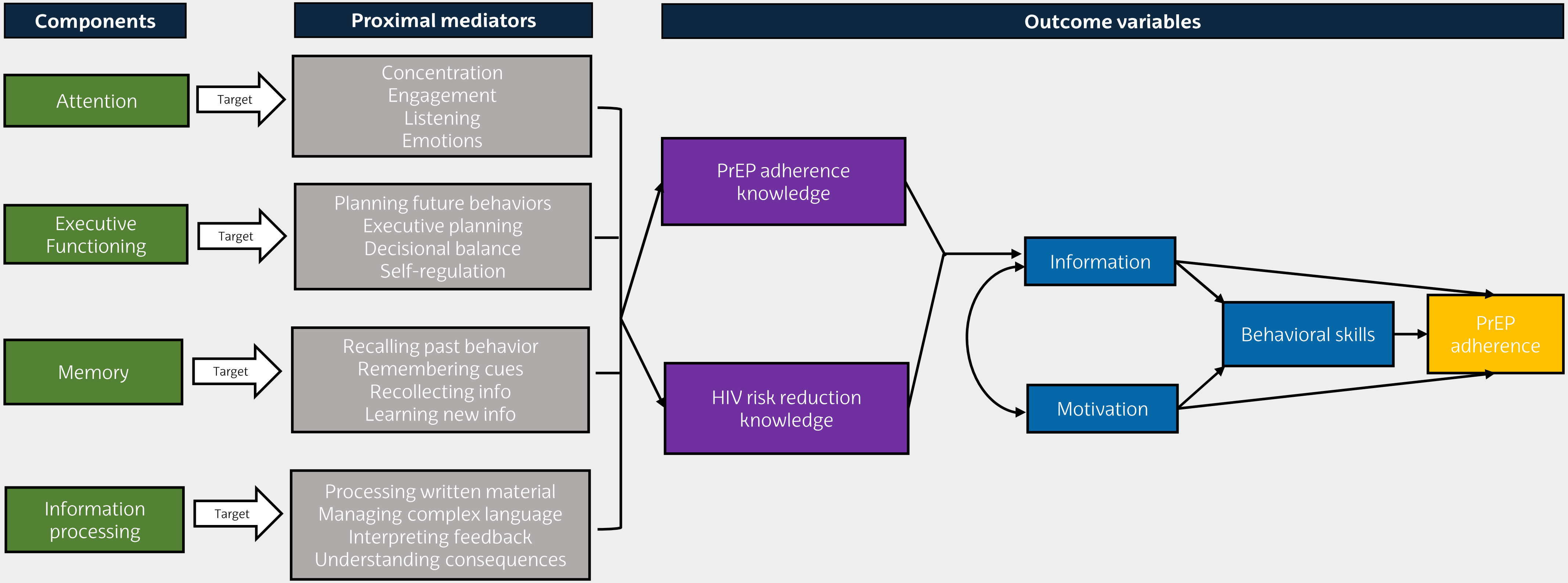
Fisher, J. D., & Fisher, W. A. (1992). Changing AIDS-risk behavior. Psychological Bulletin, 111(3), 455–474. https://doi.org/10.1037/0033-2909.111.3.455

Huedo-Medina, T. B., Shrestha, R., & Copenhaver, M. (2016). Modeling a theory-based approach to examine the influence of neurocognitive impairment on HIV risk reduction behaviors among drug users in treatment. AIDS and Behavior, 20(8), 1646-1657. https://doi.org/10.1007/s10461-016-1394-x

Parker, C. M., Hirsch, J. S., Hansen, H. B., Branas, C., & Martins, S. (2019). Facing opioids in the shadow of the HIV epidemic. The New England journal of medicine, 380(1), 1-3. https://doi.org/10.1056/NEJMp1813836

3. Application in HIV prevention study

Conceptual model



Mistler, C. B., Shrestha, R., Gunstad, J., Collins, L., Madden, L., Huedo-Medina, T., Sibilio, B., Copenhaver, N. M. & Copenhaver, M. (2023). Application of the multiphase optimisation strategy (MOST) to optimise HIV prevention targeting people on medication for opioid use disorder (MOUD) who have cognitive dysfunction: protocol for a MOST study. *BMJ open*, *13*(6), e071688. https://doi.org/10.1136/bmjopen-2023-071688

3. Application in HIV prevention study

2^4 full factorial design: Attention (*ATT*), Executive Functioning (*FUN*), Memory (*MEM*), Information Processing (*INF*).

Constant component: CHRP; *Community-friendly Health Recovery Program* (Copenhaver et al., 2013).

Five assessment points model (preintervention, postintervention, and 3-month, 6-month and 9-month postintervention follow-ups).

Condition number	CHRP	ATT	FUN	MEM	INF
1	On	On	On	On	On
2	On	On	On	On	Off
3	On	On	On	Off	On
4	On	On	On	Off	Off
5	On	On	Off	On	On
6	On	On	Off	On	Off
7	On	On	Off	Off	On
8	On	On	Off	Off	Off
9	On	Off	On	On	On
10	On	Off	On	On	Off
11	On	Off	On	Off	On
12	On	Off	On	Off	Off
13	On	Off	Off	On	On
14	On	Off	Off	On	Off
15	On	Off	Off	Off	On
16	On	Off	Off	Off	Off

3. Application in HIV prevention study

Applied mixed effects model

Level 1; within-subject model:

$$Y_{\text{adherence}ti} = \beta_{0i} + \beta_{1i}T_{ti} + \beta_{2i}Motivation_{ti} + \beta_{3i}Behavior_{ti} + \beta_{14i}Information_{ti} + e_{ti} \quad (3.1)$$

Level 2; between-subject model: Grand intercept

$$\beta_{0i} = \gamma_{00} + \gamma_{01}ATT + \gamma_{02}MEM + \gamma_{03}FUN + \gamma_{04}INF + \gamma_{05}ATTxMEM + \gamma_{06}ATTxFUN + \gamma_{07}ATTxINF + \gamma_{08}MEMxFUN + \gamma_{09}MEMxINF + \gamma_{010}FUNxINF + \gamma_{011}ATTxMEMxFUN + \gamma_{012}ATTxMEMxINF + \gamma_{013}ATTxFUNxINF + \gamma_{014}MEMxFUNxINF + \gamma_{015}ATTxMEMxFUNxINF + \gamma_{016}Age + u_{0i} \quad (3.2)$$

3. Application in HIV prevention study

Applied mixed effects model

Level 2; between-subject model: Grand slopes

$$\beta_{1i} = \gamma_{10} + \gamma_{11}ATT + \gamma_{12}MEM + \gamma_{13}FUN + \gamma_{14}INF + \gamma_{15}ATTxMEM + \gamma_{16}ATTxFUN + \gamma_{17}ATTxINF + \gamma_{18}MEMxFUN + \gamma_{19}MEMxINF + \gamma_{110}FUNxINF + \gamma_{111}ATTxMEMxFUN + \gamma_{112}ATTxMEMxINF + \gamma_{113}ATTxFUNxINF + \gamma_{114}MEMxFUNxINF + \gamma_{115}ATTxMEMxFUNxINF + \gamma_{116}Edad + u_{0i} \quad (3.3)$$

$$\beta_{2i} = \gamma_{20} + \gamma_{21}ATT + \gamma_{22}MEM + \gamma_{23}FUN + \gamma_{24}INF + \gamma_{25}ATTxMEM + \gamma_{26}ATTxFUN + \gamma_{27}ATTxINF + \gamma_{28}MEMxFUN + \gamma_{29}MEMxINF + \gamma_{210}FUNxINF + \gamma_{211}ATTxMEMxFUN + \gamma_{212}ATTxMEMxINF + \gamma_{213}ATTxFUNxINF + \gamma_{214}MEMxFUNxINF + \gamma_{215}ATTxMEMxFUNxINF + \gamma_{216}Edad + u_{2i} \quad (3.4)$$

$$\beta_{3i} = \gamma_{30} + \gamma_{31}ATT + \gamma_{32}MEM + \gamma_{33}FUN + \gamma_{34}INF + \gamma_{35}ATTxMEM + \gamma_{36}ATTxFUN + \gamma_{37}ATTxINF + \gamma_{38}MEMxFUN + \gamma_{39}MEMxINF + \gamma_{310}FUNxINF + \gamma_{311}ATTxMEMxFUN + \gamma_{312}ATTxMEMxINF + \gamma_{313}ATTxFUNxINF + \gamma_{314}MEMxFUNxINF + \gamma_{315}ATTxMEMxFUNxINF + \gamma_{316}Edad + u_{3i} \quad (3.5)$$

$$\beta_{4i} = \gamma_{40} + \gamma_{41}ATT + \gamma_{42}MEM + \gamma_{43}FUN + \gamma_{44}INF + \gamma_{45}ATTxMEM + \gamma_{46}ATTxFUN + \gamma_{47}ATTxINF + \gamma_{48}MEMxFUN + \gamma_{49}MEMxINF + \gamma_{410}FUNxINF + \gamma_{411}ATTxMEMxFUN + \gamma_{412}ATTxMEMxINF + \gamma_{413}ATTxFUNxINF + \gamma_{414}MEMxFUNxINF + \gamma_{415}ATTxMEMxFUNxINF + \gamma_{416}Edad + u_{4i} \quad (3.6)$$

3. Application in HIV prevention study

Applied mixed effects model

$$Y_{\text{adherence}ti} = \underbrace{\gamma_{00} + \gamma_{10}T_{ti} + \gamma_{20}Motivation_{ti} + \gamma_{30}Behavior_{ti} + \gamma_{40}Information_{ti}}_{\text{Level 1 fixed effects}}$$

$$\underbrace{+ \gamma_{01}ATT + \gamma_{02}MEM + \gamma_{03}FUN + \gamma_{04}INF + \gamma_{05}ATTxMEM \ldots \ \gamma_{016}Age}_{\text{Level 2 fixed effects on intercept}}$$

$$\underbrace{+ (\gamma_{10} + \gamma_{11}ATT + \gamma_{12}MEM + \gamma_{13}FUN + \gamma_{14}INF \ldots + \gamma_{116}Age) \cdot T_{ti}}_{\text{Level 2 fixed effects on Time}}$$

$$\underbrace{+ (\gamma_{20} + \gamma_{21}ATT + \gamma_{22}MEM + \gamma_{23}FUN + \gamma_{24}INF \ldots + \gamma_{216}Age) \cdot Motivation_{ti}}_{\text{Level 2 fixed effects on Motivation}}$$

$$\underbrace{+ (\gamma_{30} + \gamma_{31}ATT + \gamma_{32}MEM + \gamma_{33}FUN + \gamma_{34}INF \ldots + \gamma_{316}Age) \cdot Behavior_{ti}}_{\text{Level 2 fixed effects on Behavior}}$$

$$\underbrace{+ (\gamma_{40} + \gamma_{41}ATT + \gamma_{42}MEM + \gamma_{43}FUN + \gamma_{44}INF \ldots + \gamma_{416}Age) \cdot Information_{ti}}_{\text{Level 2 fixed effects on Information}}$$

$$\underbrace{+ u_{0i} + u_{1i}T_{ti} + u_{2i}Motivation_{ti} + u_{2i}Behavior_{ti} + u_{4i}Information_{ti}}_{\text{Level 2 random errors}}$$

$$\underbrace{+ e_{ti}}_{\text{Level 1 residual error}} \qquad (3.7)$$

4. Including equitability in intervention optimization

Interventions hold potential to (Strayhorn, 2024):

- No worse existing health disparities.
- Reduce health disparities and promote health equity.

Ensuring equity means that the benefits of interventions are distributed fairly across all population groups.

Optimizing interventions using the MOST framework—particularly in cluster-randomized trials—allows equitability to be explicitly considered and balanced alongside other factors prior to intervention evaluation.

Strayhorn, J. C., Vanness, D. J., & Collins, L. M. (2024). Optimizing Interventions for Equitability: Some Initial Ideas. *Prevention science: the official journal of the Society for Prevention Research*, *25*(Suppl 3), 384–396. https://doi.org/10.1007/s11121-024-01644-3

4. Including equitability in intervention optimization

Intervention equity

Extent to which the health benefits provided by an intervention are distributed evenly, such that all participants have a fair and just opportunity to achieve the desired outcome of the intervention (Strayhorn et al., 2024; p. 2).

Simulation studies seems to be demonstrating that defining and analyzing outcomes only at the level of the overall population can exacerbate health disparities (Guastaferro et al., 2024).

Intervening over risk populations such as PWID is a clear example of how alternative versions of an optimized multicomponent intervention **can differ in terms of equitability**.

Guastaferro, K., Sheldrick, R. C., Strayhorn, J. C., & Feinberg, E. (2024). Operationalizing Primary Outcomes to Achieve Reach, Effectiveness, and Equity in Multilevel Interventions. *Prevention science: the official journal of the Society for Prevention Research*, 25(Suppl 3), 397–406. https://doi.org/10.1007/s11121-023-01613-2

Strayhorn, J. C., Vanness, D. J., & Collins, L. M. (2024). Optimizing Interventions for Equitability: Some Initial Ideas. *Prevention science: the official journal of the Society for Prevention Research*, 25(Suppl 3), 384–396. https://doi.org/10.1007/s11121-024-01644-3

4. Including equitability in intervention optimization

Modeling considerations for equitability within hierarchical structures:

1.- In a 2 level model, like the one exposed, subgroup covariates at level 1 can be added to the model to explore the potential differentiated effects of components and their interactions across subgroups.

Subgroup variables proposed for consideration in assessing equitability in the reference intervention:

People accessing CHRP program prevalence related to (Mistler et al., 2025):

-Employment status: unemployed (35.9%) and disability, permanently or temporarily (27.4%).

-Educational level: up to some high-school (81.2%), some college degree (13.6%), higher than college (5.2%).

PrEP adherence skills moderators (disrupting the treatment effect): cognitive dysfunction level or ethnicity.

Mistler, C. B., Huedo-Medina, T. B., Shrestha, R., Gunstad, J., Zelenev, A., & Copenhaver, M. M. (2025). An Evaluation a PrEP-Focused HIV Prevention Intervention Tailored for Individuals with Opioid Use Disorder and Cognitive Dysfunction. *Neuropsychiatric disease and treatment*, *21*, 1235–1248. https://doi.org/10.2147/NDT.S490266

4. Including equitability in intervention optimization

Modeling considerations for equitability within hierarchical structures:

2.- Extending the strategic balance in intervention optimization to include equitability involves integrating metrics that reflect alternative operationalizations of success in equity terms such as (e.g.):

- Functioning among member of the PWID population with the highest levels of **cognitive impairment**.

4. Including equity in intervention optimization

Decision making considerations for equitability within hierarchical structures:

- Equitability can entail making strategic decissions such as including components that show lower overall effects in the general target population, but that are effective in reducing disparities.

  E.g. greater knowledge of HIV prevention behaviors among PWID who are permanently work disabled.

- Develop graphic representations of intervention effects by subgroups. These visuals can be used in stakeholder discussions to help identify and understand how benefits are distributed across different populations.

5. Work in progress

- Develop procedural guidelines to facilitate the adoption of factorial design in multilevel models.
- Explore the feasibility to integrate the DAIVE approach - bayesian based method (Strayhorn et al., 2024)- into multilevel decision-making models in order to optimize based on multiple outcome variable simultaneously.
- Promote equity mainstreaming as key criterion in guiding the optimization process.

Together, these strategies will support the development of **more robust and context-sensitive optimization designs** for health and social science interventions, aiming to improve access and effectiveness for at-risk populations, thereby maximizing societal impact.

Strayhorn, J. C., Cleland, C. M., Vanness, D. J., Wilton, L., Gwadz, M., & Collins, L. M. (2024). Using decision analysis for intervention value efficiency to select optimized interventions in the multiphase optimization strategy. *Health Psychology, 43*(2), 89–100. https://doi.org/10.1037/hea0001318

Thank you for your attention

I welcome your thoughts or questions

Huedo-Medina, T. B., Pérez-Setién, E., Alonso-Alberca, N., & Balluerka, N. *Multiphase Optimization Strategy (MOST) for Equitable Cluster Randomized Interventions: Design Considerations and Statistical Modeling in an HIV Application*. In prep 2025

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Funding sources:
Qualiker Research Group. PI: Dr. Nekane Balluerka, Full Professor
University of the Basque Country (UPV/EHU)
National Institute On Drug Abuse (NIDA, NIH) . Co-PIs: Dr. Copenhaver & Dr. Huedo-Medina, Ikerbasque Researcher