Grand Rounds:
The Learn As you GO (LAGO) Design

NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

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Housekeeping

- All participants will be muted upon entry
- Enter **all questions** in the Zoom **Q&A/chat box** and send to Everyone
- Moderator will review questions from chat box and ask them at the end
- Visit impactcollaboratory.org
- Follow us on LinkedIN

The Learn As you GO (LAGO) Design for Quantitative Optimization of Multi-level Multi-component Intervention Packages and Implementation Strategy Bundles

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The National Institute on Aging (NIA) Imbedded Pragmatic Alzheimer's Disease (AD) and AD-related dementias (ADRD) Clinical Trials (IMPACT) Collaboratory
Grand Rounds
February 18, 2026

Yale SCHOOL OF PUBLIC HEALTH
Center for Methods in Implementation and Prevention Science

Learn As You Go (LAGO) Designs

Nevo, D., Lok, J.J., & Spiegelman, D. (2021). Analysis of "learn-as-you-go go" (LAGO) studies. *The Annals of Statistics*, 49(2), 793-819.

Bing A, Spiegelman D, Nevo D, Lok JJ. Learn-As-you-GO (LAGO) trials: optimizing treatments and preventing trial failure through ongoing learning. *Biometrics*. 2025 Apr 2;81(2)

Bing, A., Spiegelman, D., & Lok, J. J. (2025). Learn-As-you-GO (LAGO) Trials: Optimizing Trials for Effectiveness and Power to Prevent Failed Trials. *arXiv preprint arXiv:2509.11479*.

Intervention is a package consisting of multiple components

E.g. peer mentoring (once/month),
Text message support (every other day,
Behavioral skills training (every other month),
Motivational interviewing (monthly)

Data are analyzed after each stage

Intervention package is reconfigured based on analyses,

E.g. peer mentoring (**twice**/month), Text message support (every **four** days, Behavioral skills training (**every other month**), Motivational interviewing (**every other** month)

Revised intervention package is rolled out in the next stage

Intervention package in later stages depends on the outcomes from previous stages and all data utilized for final outcome assessment

An effective intervention package is sought, while minimizing intervention package cost.

Cost of the intervention is minimized and the probability of desired outcome maximized

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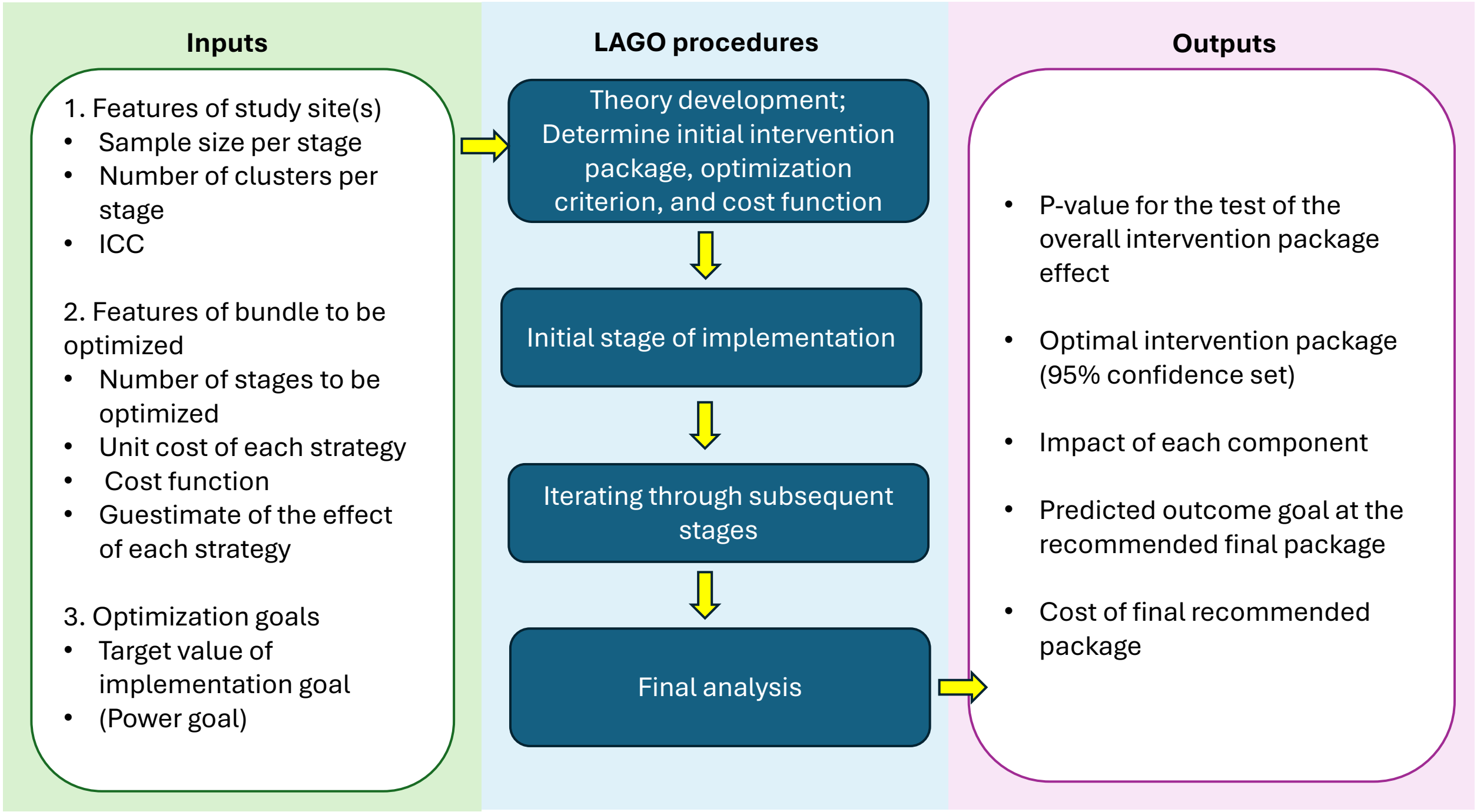

Inputs
1. Features of study site(s)
• Sample size per stage
• Number of clusters per stage
• ICC
2. Features of bundle to be optimized
• Number of stages to be optimized
• Unit cost of each strategy
• Cost function
• Guestimate of the effect of each strategy
3. Optimization goals
• Target value of implementation goal
• (Power goal)
LAGO procedures
Theory development; Determine initial intervention package, optimization criterion, and cost function
Initial stage of implementation
Iterating through subsequent stages
Final analysis
Outputs
• P-value for the test of the overall intervention package effect
• Optimal intervention package (95% confidence set)
• Impact of each component
• Predicted outcome goal at the recommended final package
• Cost of final recommended package

Steps of a LAGO study

- Preliminary steps
  - Develop a theory of change to inform the selection of the initial intervention package, $\boldsymbol{x}^{(1)}$
  - Determine optimization criteria, including desired mean outcome and lower and upper bounds on each of the intervention components
- Conduct Stage 1 of the K stages
  - Collect data on intervention strategies actually implemented, $\boldsymbol{A}_j^{(1)}$, and outcomes, $\boldsymbol{Y}_j^{(1)}, j = 1, \ldots, J$ facilities.
  - Determine unit costs of strategies in the implementation bundle
  - Determine recommended intervention for Stage 2, $\widehat{\boldsymbol{x}}^{(2)}$, based on the $\boldsymbol{A}_j^{(1)}$ and outcomes, $\boldsymbol{Y}_j^{(1)}, j = 1, \ldots, J$ facilities, and costs of Stage 1, subject to optimization criteria
- Conduct stages $k = 2, \ldots, K$ repeating the following steps:
  - Collect data on intervention strategies actually implemented, $\boldsymbol{A}_j^{(k)}$ and outcomes, $\boldsymbol{Y}_j^{(k)}, j = 1, \ldots, J$
  - Refine unit costs
  - Determine recommended intervention for Stage $k+1$, $\widehat{\boldsymbol{x}}^{(k+1)}$ based on the data collected up to stage k, ($\boldsymbol{A}_j^{(1)}$, $\boldsymbol{Y}_j^{(1)}$, $\boldsymbol{A}_j^{(2)}$, $\boldsymbol{Y}_j^{(2)}$, …, $\boldsymbol{A}_j^{(k)}$, $\boldsymbol{Y}_j^{(k)}$),, $j = 1, \ldots, J$ facilities, and costs, subject to optimization criteria
- Final data analysis using data from all K stages
  - Test the null hypothesis using outcome data from all K stages, ($\boldsymbol{Y}^{(1)}$, $\boldsymbol{Y}^{(2)}$, …, $\boldsymbol{Y}^{(K)}$)
  - Estimate the overall intervention effect and the unit effects of the individual components, using outcome and observed intervention component data from all K stages, ($\boldsymbol{A}_j^{(1)}$, $\boldsymbol{Y}_j^{(1)}$, $\boldsymbol{A}_j^{(2)}$, $\boldsymbol{Y}_j^{(2)}$, …, $\boldsymbol{A}_j^{(K)}$, $\boldsymbol{Y}_j^{(K)}$), , $j = 1, \ldots, J, k = 1, \ldots, K$
  - Estimate the final optimal intervention package, $\widehat{\boldsymbol{x}}^{(opt)}$, and its 95% confidence set, using outcomes and observed intervention data from all K stages
  - Estimate the per facility cost of the optimal intervention package and the per facility cost of the other interventions contained in 95% confidence set

LAGO table for PrEP prescribing primary outcome in HPTN 096: Getting to Zero Among Highest HIV Incidence (HHI) MSM in the American South (Chairs: LaRon E. Nelson & Chris Beyrer)

With an assumed baseline of 18% HHI MSM prescribed PrEP and a hypothesized increase to 43% HHI MSM prescribed PrEP with intervention, the overall odds ratio for the total package needs to be 2.20.

Package Component	Definition/measure	Lower, Upper bound	Intervention uptake goal	Unit Cost
Health Access Coalition	% planned coalition activities completed	0,1	0.9	TBD
Health Access Coalition	# HHI MSM direct exposure to coalition activities	0,1000	250	TBD
Social Media	# new content posted per month	0,10	5	TBD
Social Media	# Social media clicks/10,000 + # followers/1000	0,20	5	TBD
Promoting Human Autonomy Support & Empathy (PHASE)	% of eligible staff who participate in training	0,1	0.75	TBD
PHASE	# of learning launch action cycles completed	0,5	3	TBD
Peer Support	% of participants using >2 peer support sessions	0,1	0.2	TBD
Overall outcome– PrEP Rx	% of HHI MSM prescribed PrEP measured in EMR	0,1	18% --> 43% Rx	TBD

Case Study: PULESA/Uganda study of integration of hypertension care into HIV clinics in and around Kampala, Uganda

Longenecker CT, Kiggundu JB, Ayebare F, Muddu M, Kayima J, Mutungi G, Ssinabulya I, Schwartz JI, Spiegelman D, Tong G, Nugent R, Aifah A, Kagoya F, Cameron D, Hutchinson B, Kamya MR, Katahoire AR, Semitala FC.

Rationale & design of the PULESA-Uganda study: A stepped wedge cluster randomized trial of strategies to integrate HIV and hypertension care in Kampala and Wakiso Districts, Uganda.

BMC Health Serv Res **25**, 1060 (2025).

https://doi.org/10.1186/s12913-025-13281-9

Case Study: PULESA/Uganda study of integration of hypertension care into HIV clinics in and around Kampala, Uganda

Package component	Bounds	Expected OR/Unit at pre-trial	Cost estimates
Access to anti-hypertensive medicines	[0, 3]	1.5 = 50% increase in the odds of being in hypertension control for a 1 month supply prescribed to a hypertensive patient	$2.91 = cost of antihypertensive drugs dispensed / hypertensive patient/ month
Differentiated service delivery: (multi-month prescriptions)	[0,1]	1.1 = 10% increase in the odds of patients in a facility-month being in hypertension control if all blood pressure (BP) medicines were given as a multi-month prescription	$7.09 = cost of antihypertensive drugs dispensed through multi-month dispensing / hypertensive patient /month
Differentiated service delivery: (community-based drug distribution)	[0,1]	1.25 = 25% increase in the odds of patients in a facility-month being in hypertension control if all BP medicines were dispensed through the community	$2.44 = cost of antihypertensive drugs dispensed through community-based service delivery / hypertensive patient /month
Access to BP machines	[0,1]	2.1 twofold increase in the odds of being in hypertension control for each patient being measured for BP	$0.05 = cost of 1 BP measurement
Hypertension training	[0,10]	1.05 = 5% increase in the odds of being in hypertension control for every hour of training given to a provider in patient's facility	$3.97 = cost of hour of training /eligible provider /month
Performance Improvement Program	[0,1]	1.3 = 30% increase in the odds of patients in a facility-month being in hypertension control if all eligible providers participated in monthly feedback review	$2.90 = cost of performance improvement program / eligible provider/ month

Preliminary Intervention Component Data (Feb 2023-Oct 2024)

(# unique patients/total visits): 82,018/329,845)

Component	Units	Overall
Access to BP machines	Proportion of patient-visits at which BP was measured	0.73 (0.2)
Community-based blood pressure monitoring	%	0.06 (0.12)
Access to anti-hypertensive medicines	Number of 1-month supplies of anti-HTN medicine dispensed/hypertensive patient-visit/month)	1.26 (1.14)
Multi-month prescription dispensation	%	0.38 (0.33)
Hypertension training	Hours of training/eligible provider/month	0.31 (1.12)
Performance Improvement Program (x6)	Hours of sessions/month/facility	0.18 (0.38)

Set missing values to 0

Correlations Between Intervention Components
All (# unique patients/total visits): 82,018/329,845) Feb 2023-Oct 2024

All data	Access to anti-hypertensive Medicines	Access to BP Machines	Hypertension Training	Differentiated service delivery (multi-month)	Differentiated service delivery (community-based)	Performance Improvement Program
Access to anti-hypertensive medicines	1	0.35	0.05	0.65	0.22	0.35
Access to BP Machines		1	0.02	0.28	0.05	0.32
Hypertension Training			1	0.02	0.05	-0.03
Differentiated service delivery (multi-month)				1	0.21	0.25
Differentiated service delivery (community-based)					1	0.03
Performance Improvement Program						1

Blood Pressure Control %

Feb 2023 –Oct 2024	Overall	Control period	Run-in	Intervention (HTN-basic)	Intervention (HTN-Plus)
Bp control, all patients		63405/134479 = 47.15%			
BP control, clinically hypertensive patients only		1508/11010 = 13.70%			

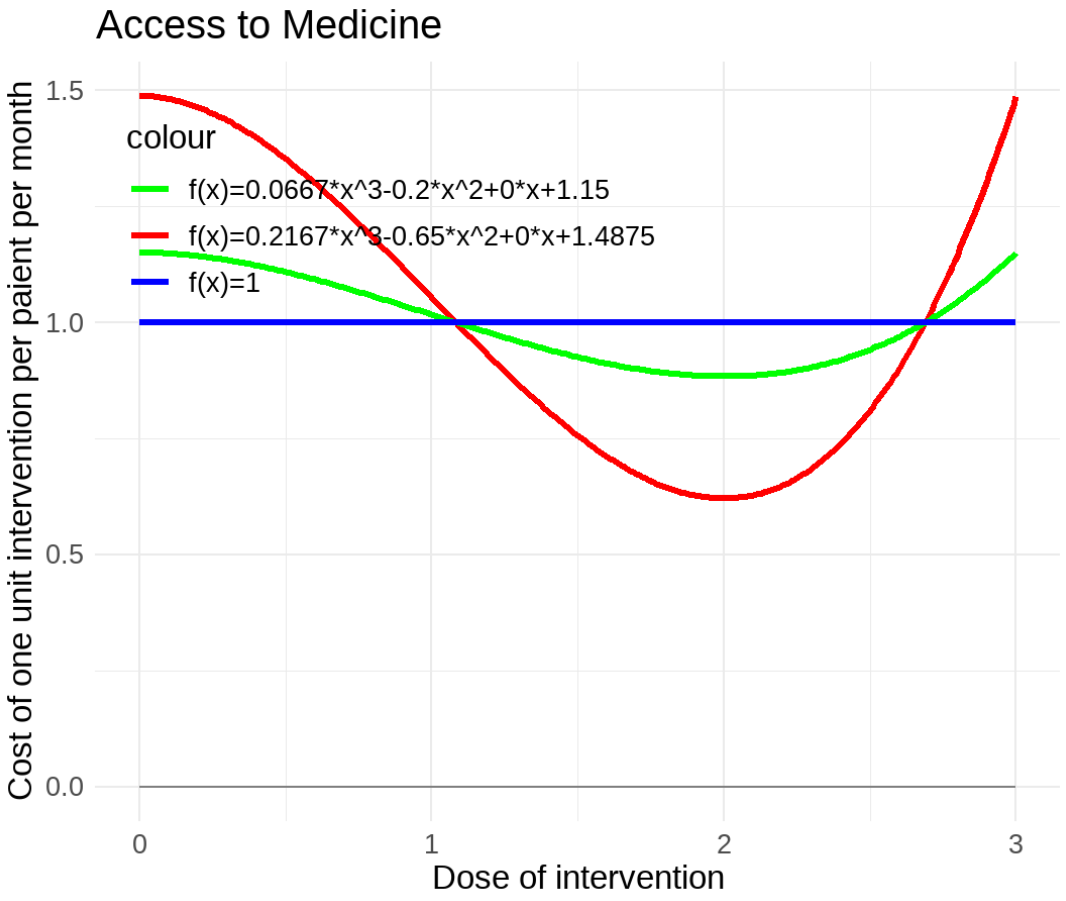
Bp control, all patients

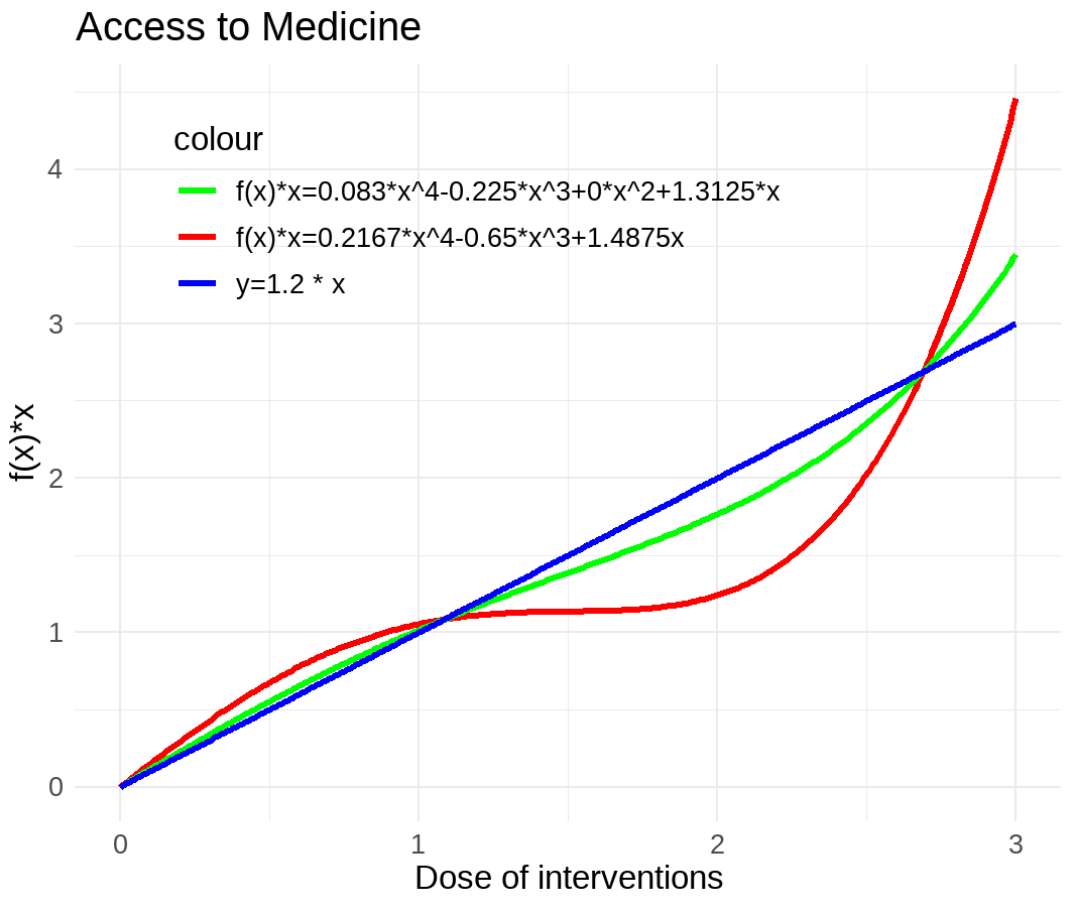
- ❑ have BP measured and blood pressure under 140/90
- ❑ includes all visits

BP control, clinically hypertensive patients only

- ❑ have BP measured and blood pressure under 140/90
- ❑ including
  - follow-up visits for participants who were hypertensive at enrollment
  - follow-up visits after participants receive a hypertensive diagnosis, i.e. clinical hypertension or two previous visits with sbp>=140 or dbp>=90

Unit Cost Function – Access to medicine





Impact Estimates for Blood Pressure Control by Individual Intervention Components: PULESA/Uganda (Semitala, Longenecker PIs)

4. Multivariate model: facility indicators, month indicators, and all the components in the model;

Package component	Units/month	All patients (N=179,628)	All hypertensive patients (N=15,811)
		OR (95 % CI) p-value	
Access to anti-hypertensive medicines	# 1 month suppliy of antihypertensive drugs dispensed to hypertensive patients	1.23 (1.20,1.27) <0.0001	1.04 (0.91,1.18) 0.584
Access to BP machines	# visits at which blood pressure is measured /patients	2.45 (2.22,2.70) <0.0001	1.54 (0.92,2.56) 0.099
Hypertension training	Hours of training /eligible provider	1.08 (1.07,1.10) <0.0001	1.09 (1.04,1.14) 0.0005
Differentiated service delivery (multi-month)	Proportion of antihypertensive drugs dispensed as a multi-month prescription/hypertensive patient	0.88 (0.85,0.92) <0.0001	1.05 (0.88,1.26) 0.575
Differentiated service delivery (community-based)	Proportion of antihypertensive drugs dispensed in the community/hypertensive patient	0.63 (0.54,0.74) <0.0001	1.69 (0.58,4.89) 0.334
Remote patient monitoring	Proportion of patients who participate in community BP monitoring	1.04 (0.85,1.27) 0.688	1.36 (0.59,3.11) 0.469
Performance Improvement Program	Proportion of eligible providers participating in performance improvement planning after monthly audit & feedback on cascade metrics/ month	1.16 (1.07,1.26) 0.0003	1.85 (1.41,2.41) <0.0001

Yellow highlight shows effects that differ between all patients and hypertensive patients

Optimization criteria

- Achieve 80% blood pressure control among all patients (up from 47% at baseline)
- Achieve 80% blood pressure control among hypertensive patients (up from 14% at baseline)
- Find the combination of doses of these 6 components that achieves these two goals at lowest cost
- (Find the combination of doses of these 6 components that achieves these two goals and provides at least **80% power** for the test of the difference between hypertension control rates between control and intervention arms at the end of the study)
    - Bing, Ante, Donna Spiegelman, and Judith J. Lok. "Learn-As-you-GO (LAGO) Trials: Optimizing Trials for Effectiveness and Power to Prevent Failed Trials." *arXiv preprint arXiv:2509.11479* (2025).

Preliminary PULESA/Uganda LAGO Optimization: Integration of Hypertension Care into HIV Clinics

Minimum cost intervention package to achieve 80% population hypertension control

Preliminary PULESA/Uganda LAGO Optimization: Integration of Hypertension Care into HIV Clinics in Uganda

Intervention Component (Units)	Observed Dose Mean (SD)	Recommended Dose	Cost by component
# Antihypertensive drugs dispensed (1 month supply) /hypertensive patients seen in past month	2.23 (0.70)	1.5	$4,336 (74%)
Proportion of antihypertensive drugs dispensed as a multi-month prescription/patient/month	0.52 (0.22)	N/A	
Proportion of antihypertensive drugs dispensed through community-based drug distribution model/patient/month	0.08 (0.13)	N/A	
Proportion of patients/month getting htn medicine in the facility as single month		0.03	
Proportion of patients/month getting htn medicine in the facility as multi-month		0	
Proportion of patients/month getting htn medicine in the community as single month		0.97	
Proportion of patients/month getting htn medicine in the community as multi-month		0	
# blood pressures measured/patients seen in past month	0.83 (0.11)	0.66	$1,155 (20%)
Hours of training (per month)/eligible provider	0.27 (0.42)	5.4	$282 (5%)
Proportion of eligible providers participating in performance improvement planning after monthly audit & feedback on cascade metrics/ month	0.64 (0.48)	0.81	$66 (1%)
Total cost for all facilities per month		$5,839	
Estimated Outcome Rate (All patients)		0.83	
Estimated Outcome Rate (Hypertensive patients)		0.80	

What Research Questions Does LAGO Answer?

- Effectiveness Question: Did the adapted and refined intervention improve outcomes vs. control?
- Optimization Question: What is the most cost-effective combination of components and dosages to achieve a target goal?
- Component Question: Which specific components drove success, and by how much?

How Do We Interpret Results from a LAGO study?

- Global Test: Compares LAGO –adapted intervention vs. control; significance shows adaptive framework outperforms standard of care.
- Optimal Package: Model estimates lowest-cost combination achieving the goal.
- Confidence Set: Includes alternative packages statistically likely to succeed
- Application: Policymakers can select feasible packages or estimate optimal packages for new contexts.

Non-technical manuscript in progress

“Optimizing Complex Health Interventions with the Learn As You Go (LAGO) Design”.

Donna Spiegelman, Dong (Roman) Xu, Ante Bing, Guangyu Tong, Mona Abdo, Jingyu Cui, Charles Goss, John Baptist Kiggundu, Chris T. Longenecker, LaRon Nelson, Drew Cameron, Fred Semitala, Xin Zhou, Judith J. Lok

Email me to get a copy once we post it on–line

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Work in progress – more to do

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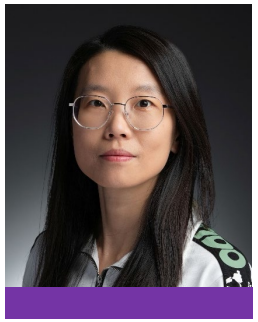
- publicly available software for LAGO optimization
- developing methods and software for optimal design of LAGO studies
- extensions of LAGO to multi-level data, survival data, general link functions (odds ratio, risk ratio, risk difference, difference in means, ratio of means)
- Control for confounding due to random- and non-random adherence to protocol
- Q-LAGO – incorporating qualitative information at each stage to inform recommended package for the next stage
- Applications to PULESA, TASKPEN, MAP-IT, Medly, HPTN-096.

Judith Lok (BU), **Jingyu Cui** (Yale BIS Post-doc), **Ruyi Liu** (Yale Implementation Science Pathway BIS PhD student), **Xin Zhou, Drew Cameron** (Yale), **Ante Bing** (BU BIS PhD student)


Judith Lok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Ruyi Liu

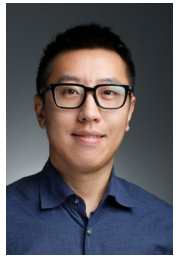

Xin Zhou


Drew Cameron

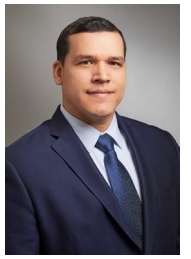
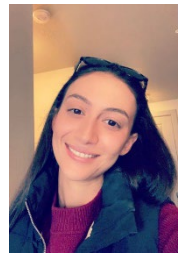

Ante Bing

Yale's Center on Methods for Implementation and Prevention Science: What we do (https://ysph.yale.edu/cmips/)





- Cluster randomized trial design, management and analysis
- Stepped wedge design, management and analysis
- LAGO
- Hybrid Type 1-3 designs
- MOST
- Mixed methods
- Qualitative research
- Economic evaluation and costing
- Implementation science theory, models and frameworks
- Causal inference
- External validity
- Longitudinal study design and analysis
- Survival study design and analysis
- Database design and data management
- HIV/AIDS, NCDs, mental health, maternal and child health

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Questions?