

WEBINAR



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Rescuing Low Accrual Clinical Trials with Generative Models

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Original Paper

Augmenting Insufficiently Accruing Oncology Clinical Trials Using Generative Models: Validation Study

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Recruiting patients for clinical trials is hard!

25% of clinical trials are discontinued before completion and the **number one cause is challenges in patient recruitment.**

In adult cancer trials, between 20% and 50% fail to complete or were unable to reach recruitment goals.

A huge priority of clinical trial design is to optimize for cost effective recruitment of participants.



Selecting the 'right' patient population

- Defining inclusion & exclusion criteria to patients that may see a clinical benefit
- Use RWD sources to quantify prevalence



Optimizing site selection

- Sites with experienced clinician investigators
- Sites that can provide all care required in the study protocol



Streamlining recruitment process

- Pragmatic trial design to reduce the burden on participants
- Clear educational materials for both clinicians and patients



Innovative study designs

- Single arm studies with External Control Arms (ECAs) to lower recruitment targets
- Bayesian trial designs without fixed recruitment targets

Even the most well designed trials may struggle to recruit

Recruitment can struggle due to:

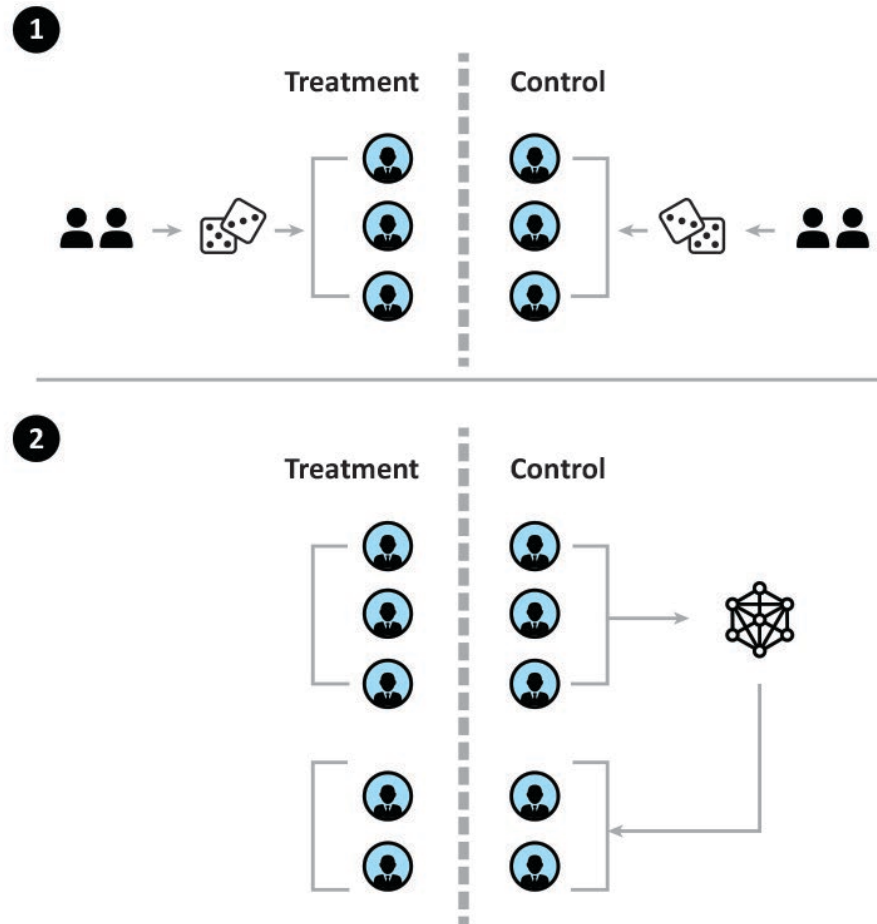
- Poor understanding of the benefit to participants
- Poor site selection with limited eligible participants to recruit
- Large scale disruptions to healthcare (e.g., COVID -19 pandemic)
- Running out of funding or withdrawal of funding for the study

This can lead to early termination, where researchers have to attempt to analyze the data collected to date.

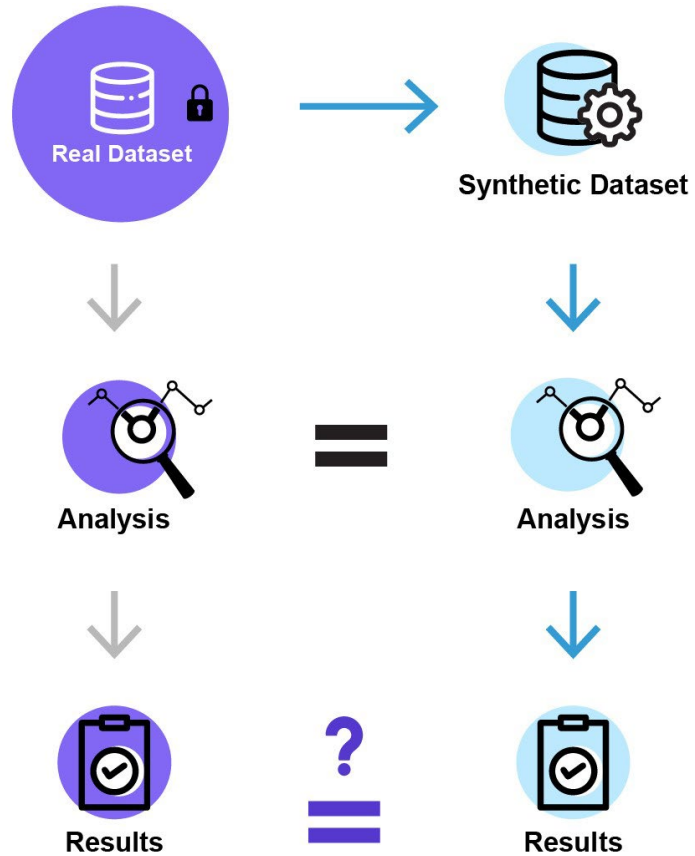
These incomplete trial dataset are underpowered and difficult to use to draw statistically significant treatment effects

Can Generative models and synthetic data be used to draw better conclusions from underpowered studies?

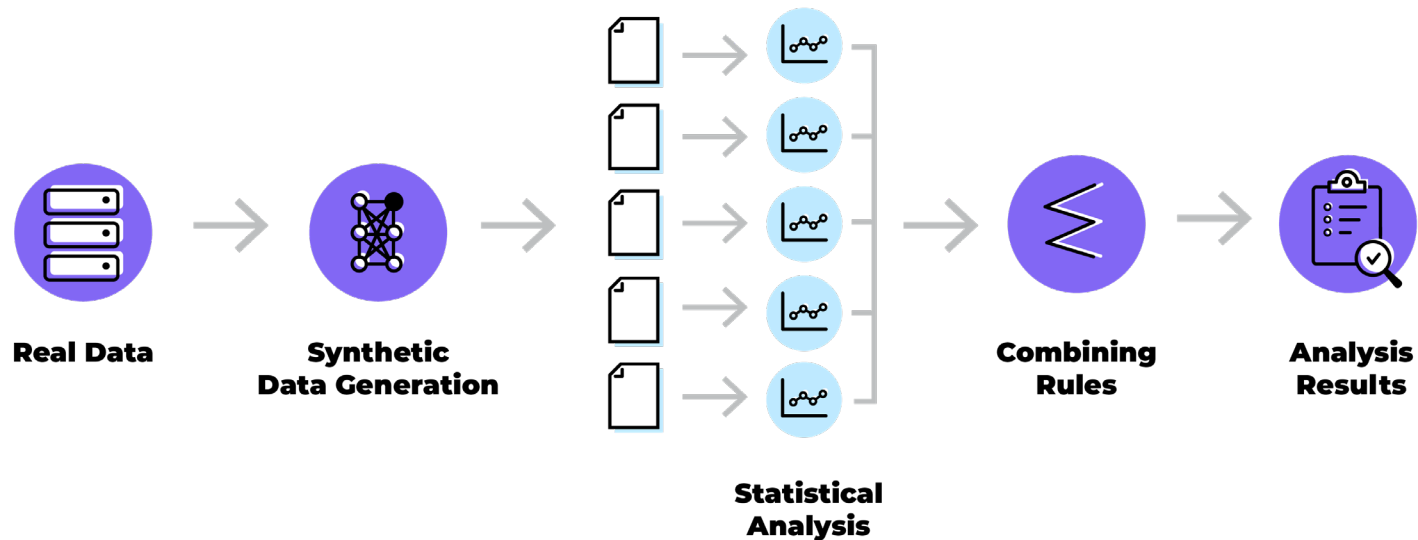
Insufficient accrual in clinical trials



Replicability of results



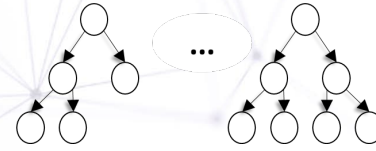
Because synthesis introduces additional variation, this needs to be accounted for to get valid estimates



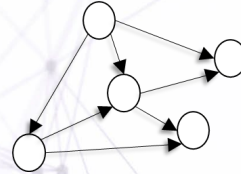
Dataset	NCT identifier	Participants, N	Variables in dataset ^a , n	Strata info?	Control arm	Patients in the control arm, n (%)	Treatment arms considered	Patients in the treatment arm, n (%)	Enrollment period
RE-aCT ^b -ILI-AD	NCT02861859	218	8	True	Placebo	105 (48)	Active olanzapine	113 (52)	December 2016 to June 2019
REaCT-BTA ^c	NCT02721433	230	8	True	4 weekly BTA	118 (51)	12 weekly BTA	112 (49)	August 3, 2016, to June 5, 2018
CCTG ^d MA27	NCT00066573	7576	25	True	Anastrozole	3787 (50)	Exemestane	3789 (50)	June 2, 2003, to July 31, 2008
NSABP ^e B34	NCT00009945	3310	49	True	Placebo	1656 (50)	Clodronate	1654 (50)	January 22, 2001, to March 31, 2004
REaCT-G/G2	NCT02428114 and NCT02816164	401	10	True	7 or 10 d of granulocyte colony stimulating factor	248 (62)	5 d of granulocyte colony stimulating factor	153 (38)	May 2015 to September 2018
REaCT-HER2 ^f	NCT02632435	50	47	True	Peripherally inserted central catheter	26 (52)	PORT; totally implanted vascular access device	24 (48)	March 2016 to March 2018
ABC-SG ^g -12	NCT00295646	1803	35	False	Tamoxifen ^h	900 (50)	Anastrozole ^h	903 (50)	1999 to 2006
REaCT-ZOL ⁱ	NCT03664687	211	11	False	— ^j	—	—	—	November 1, 2018, to April 2, 2020
SWOG ^k 0307 ^l	NCT00127205	6018	23	False	Clodronate	2268 (38)	Zoledronic acid	2262 (38)	January 2006 to February 2010

Generative AI Models

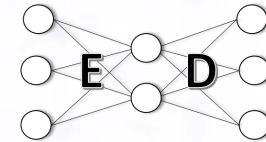
Sequential Decision Trees (SEQ)



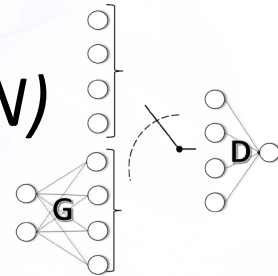
Bayesian Network (BN)



Tabular Variational Autoencoder (TVAE)

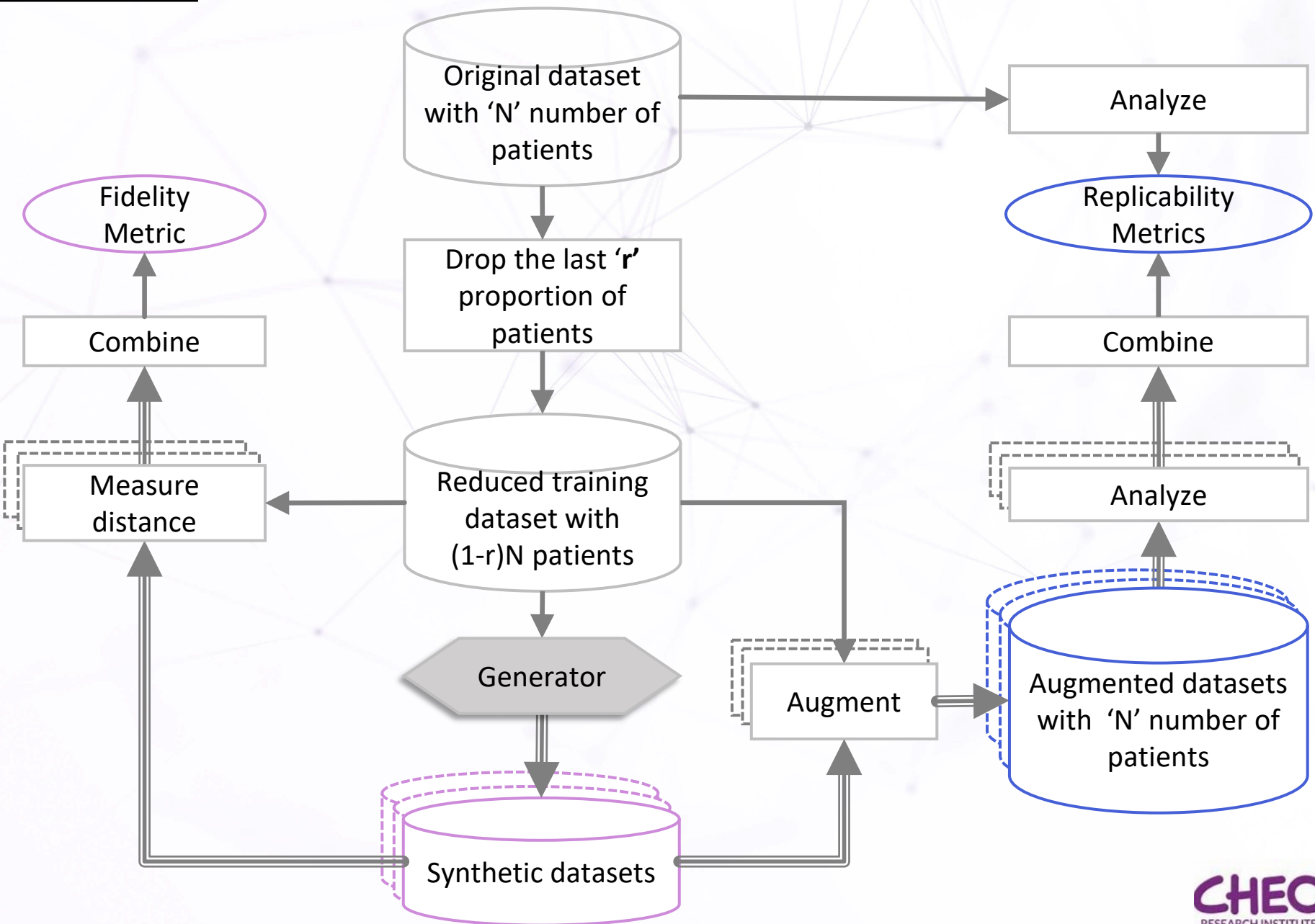


Conditional Generative Adversarial Network (CTGAN)

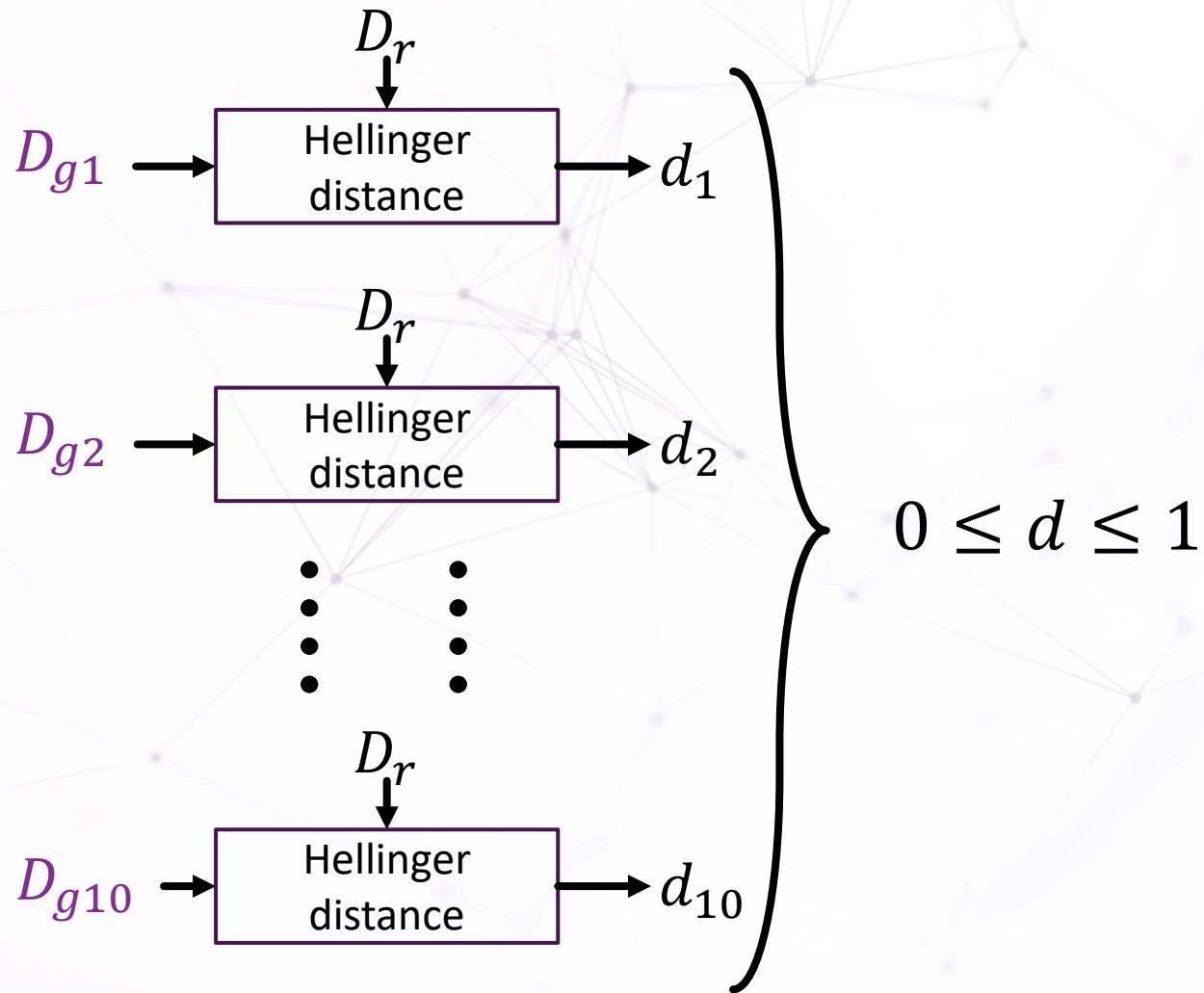


Bootstrap

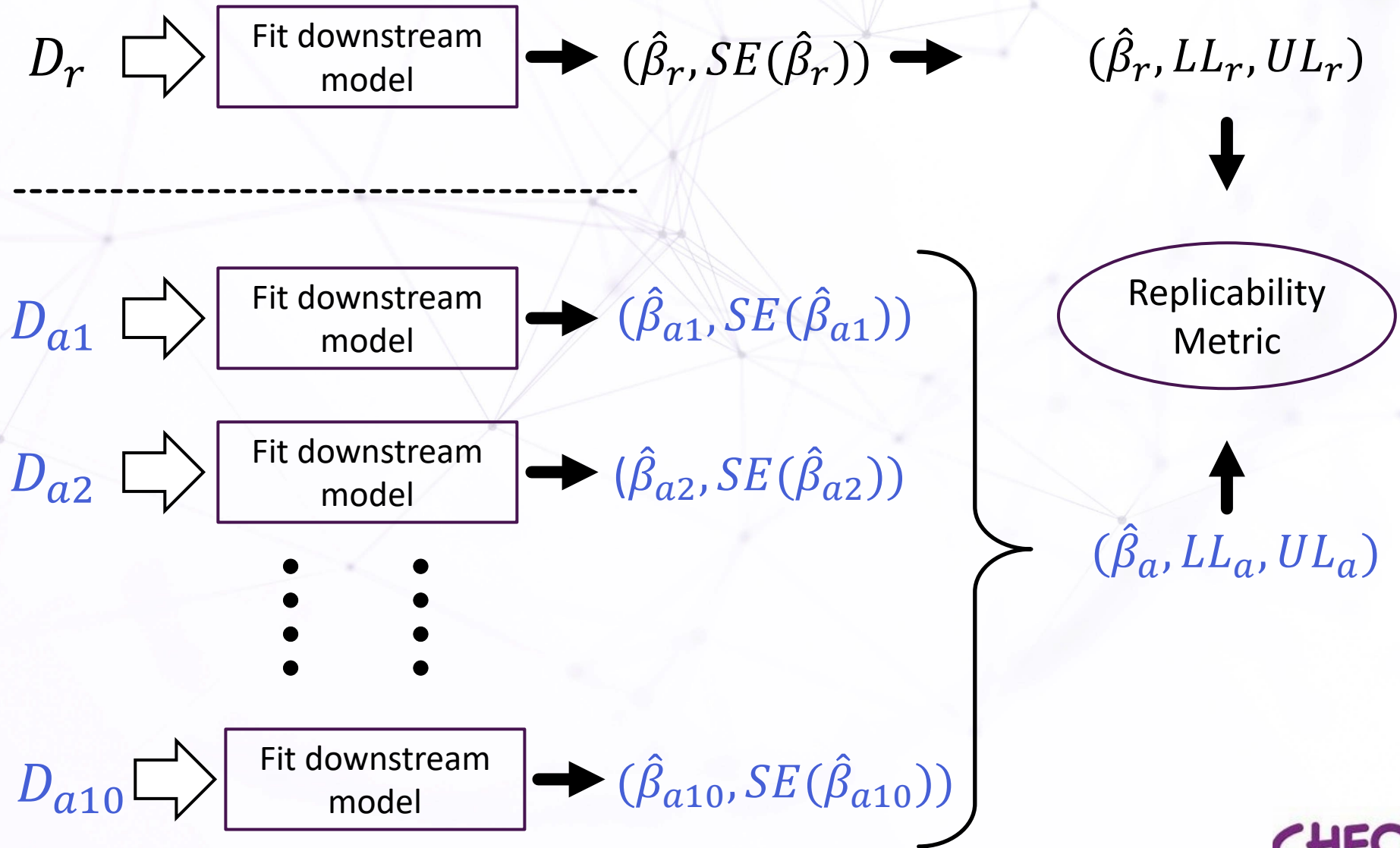
Method



Fidelity metric

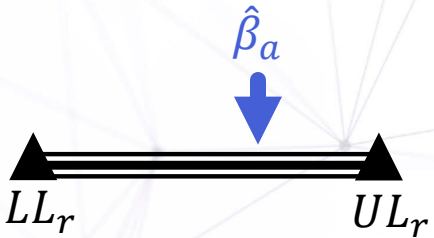


Downstream analysis

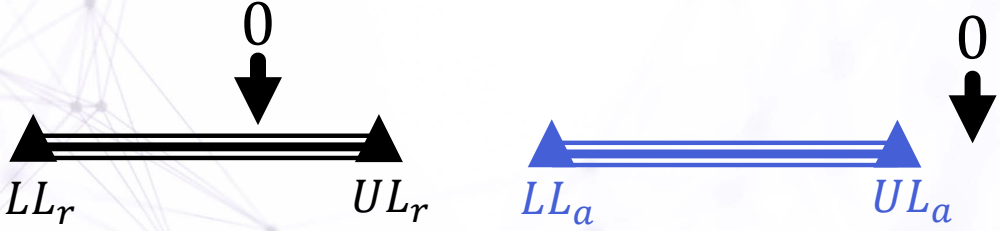


Replicability Metrics

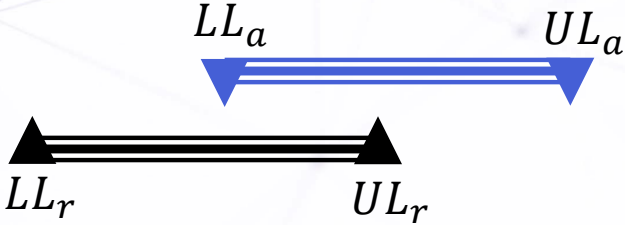
Estimate agreement



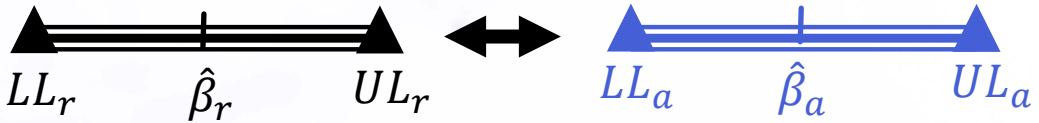
Decision agreement



CI overlap



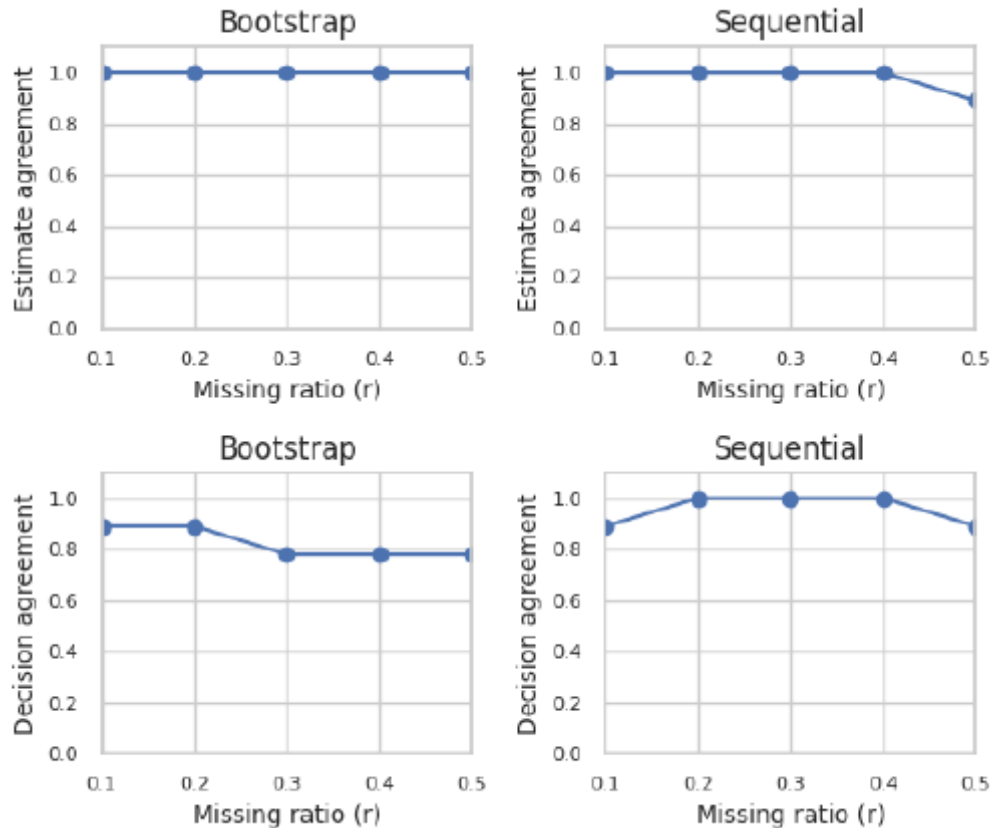
Standardized difference



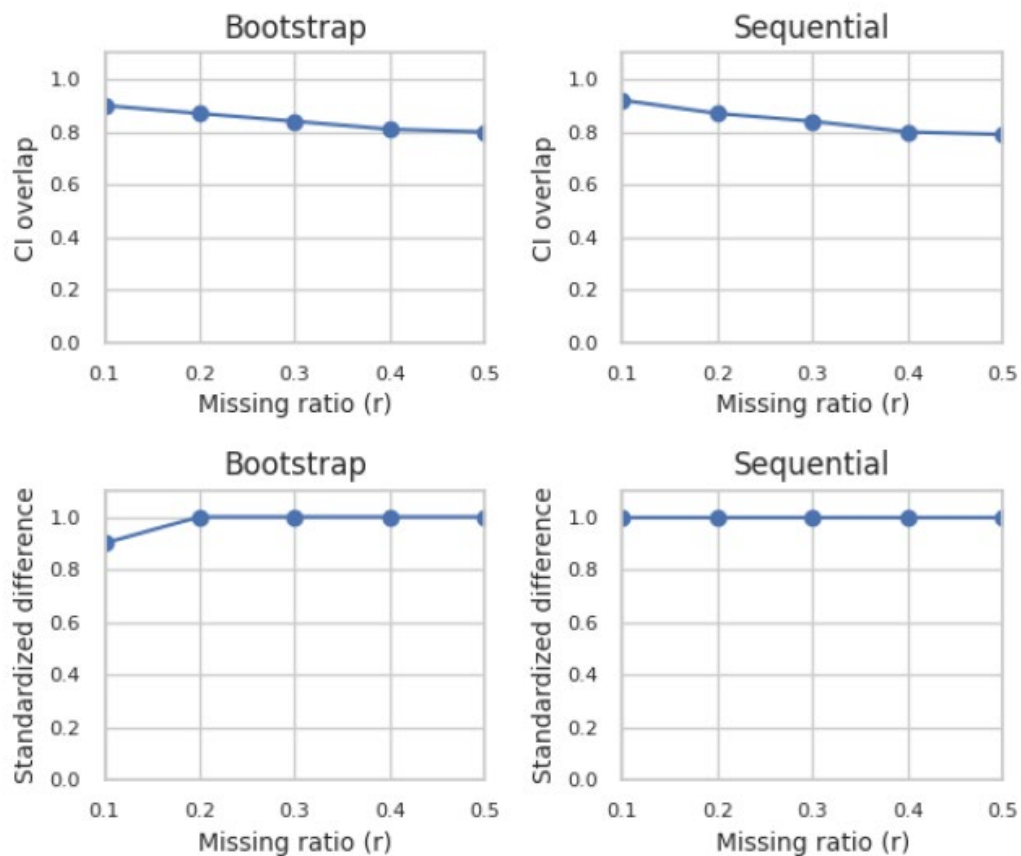
Order effect ?

Trial	Main effect (95% CI)	Interaction effect (95% CI)
REaCT ^a -ILIAD	0.52 (0.023 to 1.01)	-0.00000371 (-0.0000116 to 4.16×10^{-6})
REaCT-BTA ^b	-1.85 (-4.75 to 1.04)	0.011 (-0.032 to 0.0542)
CCTG ^c MA27	0.033 (-0.117 to 0.18)	-0.0000135 (-0.0000854 to 5.84×10^{-5})
NSABP ^d B34	-0.036 (-0.18 to 0.11)	8.28×10^{-5} (-0.000072 to 0.00024)
REaCT-G/G2	0.015 (-0.0019 to 0.032)	6.6×10^{-6} (-0.000005 to 1.85×10^{-5})
ABC SG ^e -12 (tamoxifen vs anastrozole)	0.11 (-0.13 to 0.35)	7.36×10^{-5} (-0.0004 to 0.00054)
ABC SG-12 (zoledronic acid vs no zoledronic acid)	-0.24 (0.48 to 0.002)	6.69×10^{-5} (-0.00041 to 0.00054)

Insufficient accrual in clinical trials – results (1/2)



Insufficient accrual in clinical trials – results (2/2)



Limitations

- This work only used completed breast cancer trials, findings need to be reproduced in other therapeutic areas
- Marginal treatment effects were more difficult to reproduce
- Only looked at treatment effect not safety data
- Certain generative models require more data to train so may not be suitable for small trials with low recruitment → pre-trained generative models may be better suited for these types of small trials
- Only looked at trials that had truly completed, there may be confounding differences in characteristics of trials that do vs do not hit their recruitment targets that limit the generalizability of these findings

Future of clinical trial augmentation with synthetic data

If the limitations of our findings are addressed in future research

For sponsors & CROs

- A broader set of analytic tools to gain meaningful insights from trials that are discontinued early
- More cost effective clinical trials
- *Augmenting control arms to lower recruitment targets and use alternate allocation ratios*
- *Prospectively design trials with lower recruitment targets due to synthetic data*

For patients

- Participant data from discontinued trials are better used
- *Rare disease trials that may have very long recruitment windows could gain insights sooner*
- *New drugs are able to come to market sooner to help patients with conditions that have few treatment options*

For regulators

- Receive submissions that include evidence from trials rescued with synthetic data
- *Prospectively lower recruitment targets with synthetic data*

Italicized use cases are being validated through active research!



QUESTIONS