



Single Day Event

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Challenges in developing datasets for **Synthetic Control Arm**



Here we go...

- ✓ SCA overview
- ✓ SCA: Benefits
- ✓ SCA: Implementation
- ✓ CDISC and SCA
- ✓ Future Direction



Overview: Synthetic Control Arm (SCA)

Challenges faced by sponsors

Large number of patients needed

Higher dropout rate

Fear of getting placebo

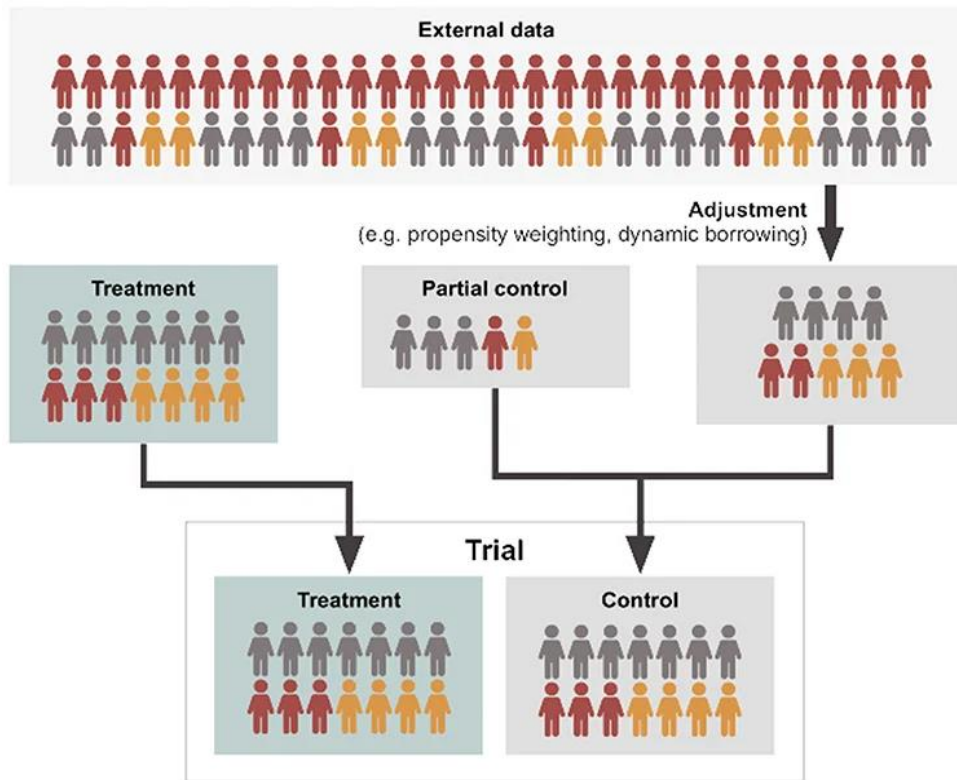
The approach, an alternative

Can we use **existing data**
for **control arm**?

Approach:

Synthetic Control Arm (SCA)

Overview: Synthetic Control Arm (SCA)



Previous clinical studies + RWD

Control candidates, match & compute

Control patients

Synthetic Control Arm



SCA: Benefits

Improved
patient
recruitment

Reduce delays

Lower
trial cost

Improved
patient
retention

Reducing the
need to enroll
control
participants

Eliminate the
risk of
unblinding

Speeding
lifesaving
drugs to
market

Large
control
group



SCA: Implementation

Get the data in the required format



Data: Harmonization, standardization



Statistical analysis



SCA: Implementation (Cont.)





CDISC and SCA

	Regular RCT	SCA
Available information	Study Protocol ✓ Annotated CRF ✓	Study Protocol ✗ Study design ✓ Annotated CRF ✗
SDTM & ADaM Guidelines	Study Submission ✓	Integration ✗
ADaM	SAP ✓	SAP ✗
Submissions	Define Package ✓	Define Package ✓

Examples

- The FDA approved cerliponase alfa for a specific form of Batten disease, based on synthetic control study that compared the data of 22 patients studied in a single-arm trial versus independent external control group data with 42 untreated patients.¹
- Across 20 European countries, alectinib, a non-small cell lung cancer treatment, had an expansion of label based on synthetic control study based on an external data set of 67 patients.²
- A kinase inhibitor, palbociclib, also had an expanded indication for men with HR+, HER2-advanced or metastatic breast cancer on the basis of external control data.³

1. FDA approves first treatment for a form of batten disease [press release]. Online, April 2017.

2. Petrone J. Roche pays \$1.9 billion for Flatiron's army of electronic health record curators. *Nat Biotechnol.* 2018;**36**(4):289–290. doi:10.1038/nbt0418-289 [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]

3. Stalder RZ, Wrobel BJ, Boehncke L, Brembilla W-H, Costantino N. The janus kinase inhibitor tofacitinib impacts human dendritic cell differentiation and favours M1 macrophage development. *Exp Dermatol.* 2019;**12**:12. [[PubMed](#)] [[Google Scholar](#)]

Future direction

FDA

- Accepted the use of external controls*
- Approved the possibility of hybrid approaches[#]

EMA

- Endorsed a joint statement- collaboration to integrate RWE into regulatory decision-making**
- Recognized and taken initiatives to allow novel approaches to external control data^{##}

* Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials. Available at: <https://www.fda.gov/media/71349/download>

Draft Guidance for Industry: Rare Diseases: Natural History Studies for Drug Development. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development>

**<https://www.ema.europa.eu/en/news/global-regulators-call-international-collaboration-integrate-real-world-evidence-regulatory-decision>

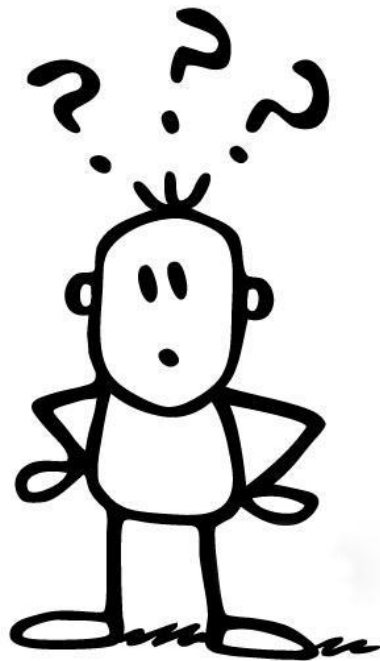
##https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf



Conclusion

- ✓ RCT is the gold standard
- ✓ Randomization may not be feasible
- ✓ The use of external controls 
- ✓ Synthetic Control Arm (SCA)
 - Reduce the patient burden
 - Flexibility to use historical/synthesized data
- ✓ Challenges with CDISC and SCA
 - Need to have an excellent understanding of databases, source datasets

Questions?





**The Global Healthcare
Data Science Community**

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