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Single Day Event

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Introduction to Synthetic Control Arm

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Background

Healthcare Systems

Goal: Bring better treatments faster, cheaper to market with the least burden on patients

Approach: Technology & innovation is the key to achieving success in all aspects

- *Discovery*
- *Development*
- *Treatment*
- *Continuing care*

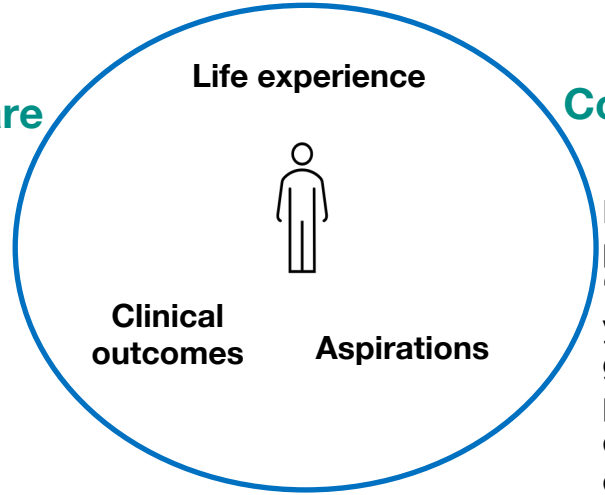
A key mantra that the healthcare systems across the globe have adopted to achieve their goals is

PATIENT CENTRICITY

Patient Centricity

Quality of Care

Achieving patient centricity, the process of designing a service or solution around the patient, has been difficult



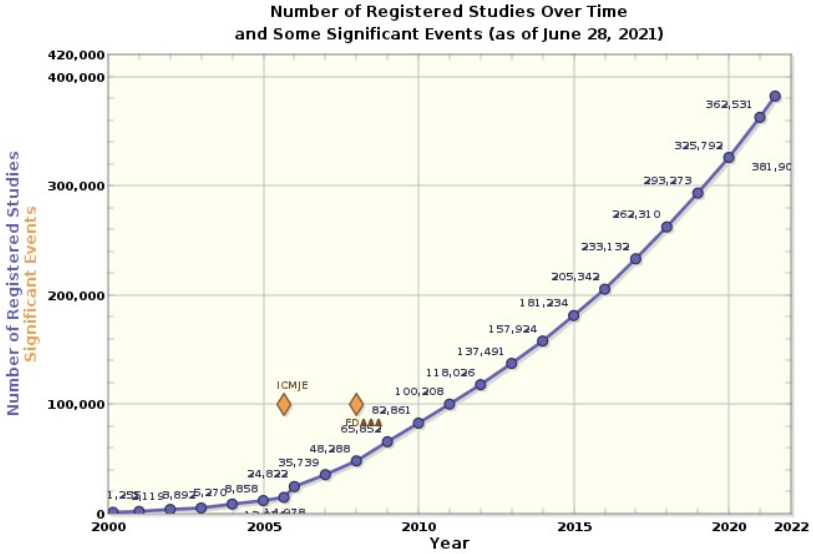
Cost of care

But what does it mean to be patient-centric?
“When you get to the point when you can’t do anything without getting a discussion with patients, that’s when you’ve embraced the concept, for example, you can’t write a protocol without getting patients’ input”

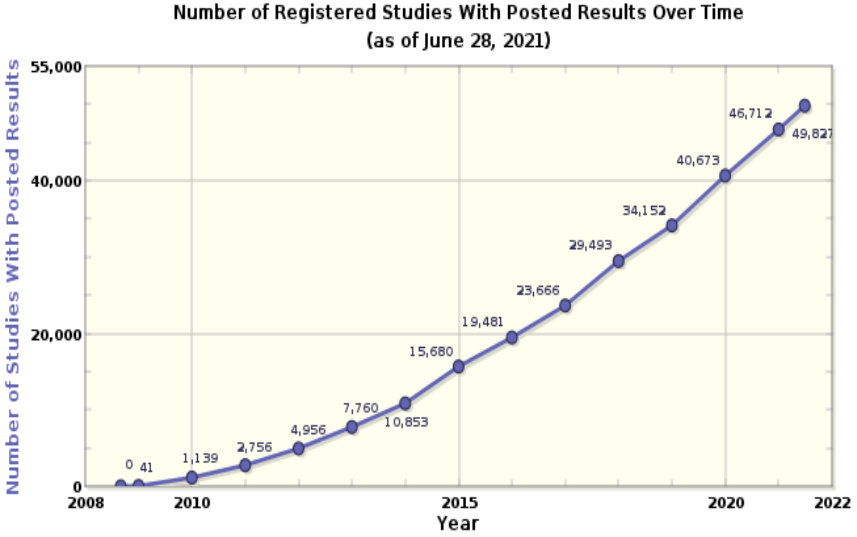
Logistics of Care

Can patient centricity have the unintended consequence of increasing patient burden in a clinical trial setting?

Clinical Trial Trends



Source: https://ClinicalTrials.gov



Source: https://ClinicalTrials.gov

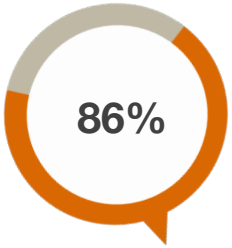
https://clinicaltrials.gov/ct2/resources/trends

Patient recruitment - Statistics

Recruitment timelines

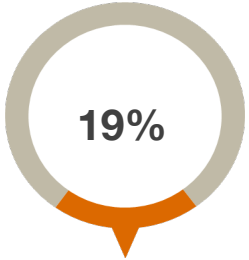
According to the **National Institutes of Health (NIH)**, more than 80% of *clinical trials in the United States fail to meet their patient recruitment timelines*. These delays increase costs, may deplete resources, and prolong the time to enter the market

Recruitment targets



Clinical trials *do not reach recruitment targets* within their specified time periods

Early Trial termination



According to an analysis of registered trials, *19% trials were closed or terminated early because they could not accrue enough participants*

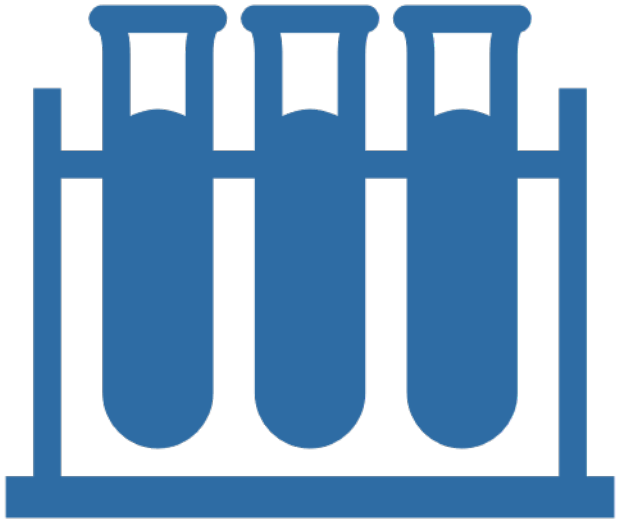
Trial timelines

According to the FDA, only six percent of clinical trials are completed on time, and 80% of all trials are delayed at least one month because of unfulfilled enrollment.

https://credevo.com/articles/2020/03/31/how-to-improve-patient-recruitment-in-clinical-trials/

Challenges faced by Sponsors

- Increasing number of trials - the large number of participants needed for trials
  - Many clinical trials struggle with both enrollment and patient retention.
  - 80% of trials struggle with enrollment
- Willingness to participate is decreasing - participants **fear they will be end up getting a placebo**
  - Some studies estimate that up to 30% of patients who join a clinical trial end up dropping out



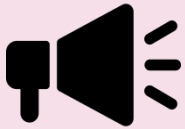
So, the question is:

How can we be patient centric when conducting clinical trials?

Patient Centricity in Trial Design

Host a patient group

Patients can give the best insight on how disease symptoms impact their daily lives. Understanding the kinds of treatments that would make a meaningful difference can help greatly with both designing the trial and positioning it when you're ready to enroll patients



Work with patient advocacy organizations

Patient Advocacy Groups also offer valuable insights into how patients will respond to both the goal and the logistics of your trial

Use existing data

When designing your trial, look at patient data from previous trials or trial searches to understand protocol issues that may have slowed down or stalled past research, such as eligibility criteria that do not reflect real-world patients

https://www.antidote.me/blog/what-is-patient-centricity

Leverage Existing Data

Use Existing data

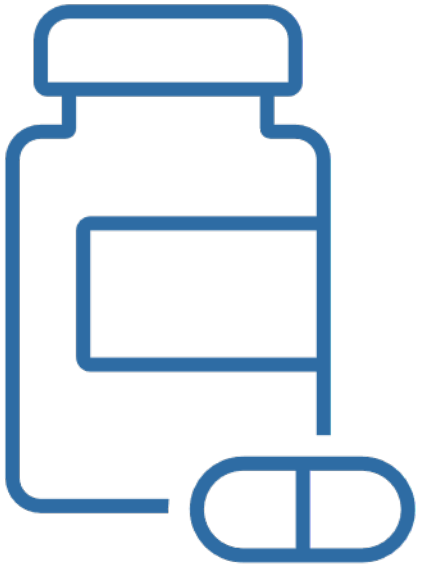
- Can existing data be used to augment or replace the placebo arm?
- Can we use existing data to serve as a control arm for single arm trials that are driven by ethical concerns and lack of patients (e.g. rare disease)

Presenting:

Synthetic Control Arm

SCA for Rare Diseases

- Randomized Control Trials are gold-standard for regulatory submissions, but in some cases, they are either infeasible or unethical
  - For rare diseases with small patient populations information from real-world data sources can help create a comparison arm and remove barriers to approval
  - When a single arm trial is implemented by necessity, a synthetic control arm can play an important role for augmenting data collected for submission



Synthetic Control Arm – *Introduction*

Synthetic Control Arm – *How does it work?*

Instead of collecting data from patients recruited for a trial who have been assigned to the control or standard-of-care arm, synthetic control arms model those comparators using real-world data that has previously been collected from sources such as health data generated during routine care including

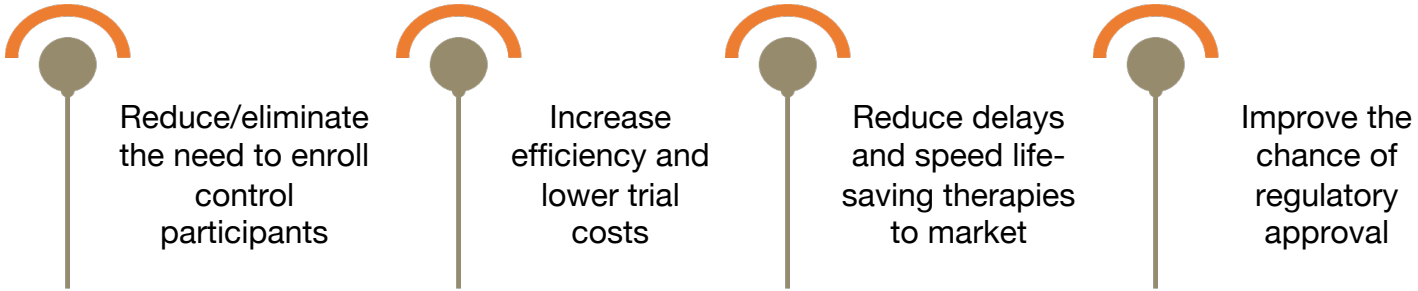
- electronic health records
- administrative claims data
- patient-generated data from fitness trackers or home medical equipment
- disease registries
- historical clinical trial data.

Synthetic Control Arm – *Concepts & Benefits*

Concepts

Synthetic control arms can augment single arm clinical trial data without the ethical and numerical enrolment challenges of a placebo controlled randomized control trial. SCAs can deliver the results with as low as 25 patients for a trial design with reduced costs.

Benefits:

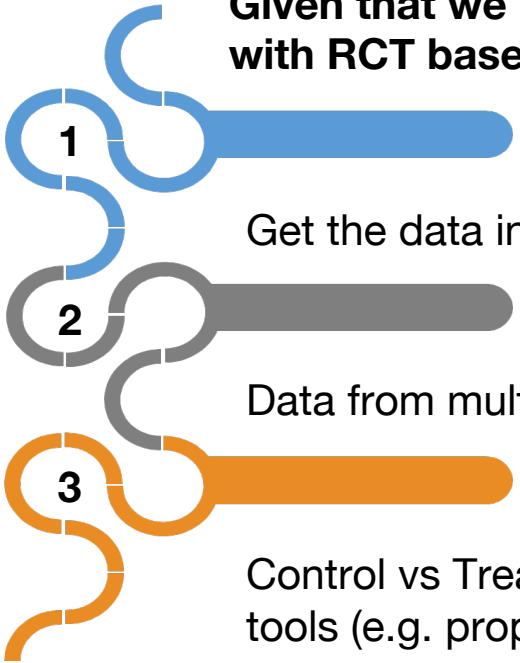


Synthetic control arm can increase efficiency, reduce delays, lower trial costs, and speed lifesaving therapies to market. For example, a trial that needs to include have 500 participants in the treatment arm to demonstrate efficacy. Instead of having to recruit 1,000 patients — 500 for the active arm, 500 for the control arm — only 500 participants need to be recruited when a synthetic control arm is employed

Implementation and Analysis

Synthetic Control Arm – *Process overview*

Given that we have a synthetic control arm, how do you compare with RCT based treatment arm



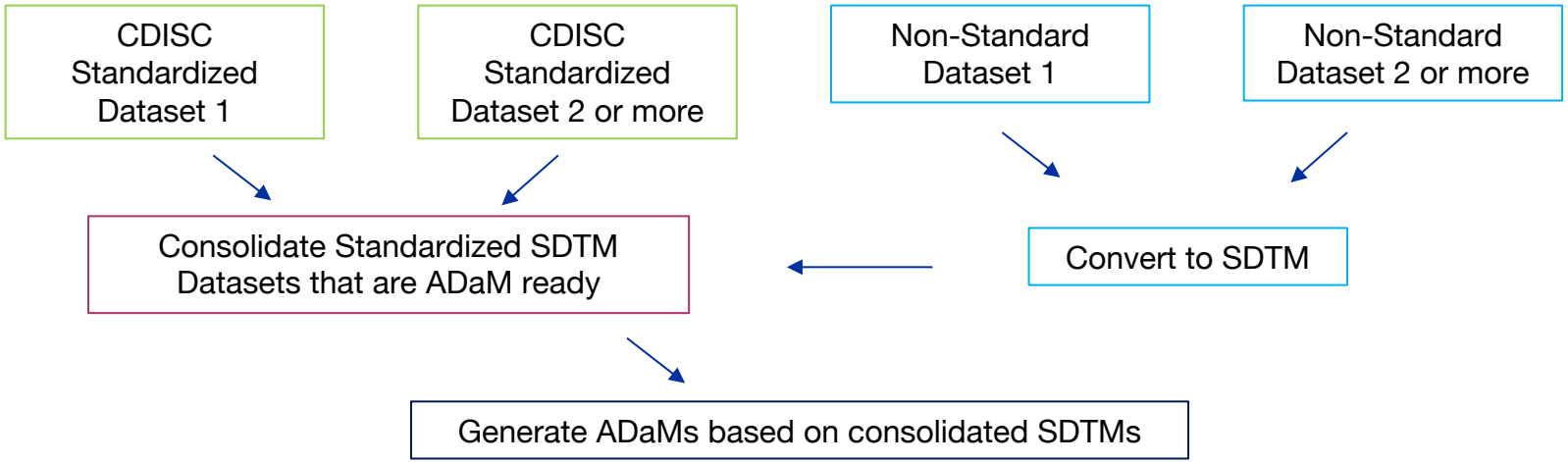
Get the data in the right format

Data from multiple sources need to be harmonized as well as standardized

Control vs Treatment comparison has to be handled using statistical tools (e.g. propensity scores, Bayesian)

Existing Data – *Standardized vs Non-Standardized*

Source for generating SCA datasets can either be from an already CDISC standardized dataset or from other non-standardized sources such as EHR, hospital and claims data.



Synthetic Control Arm – *Submission Phase*

Source Data Extract

Multiple Studies Source Extract with typically hundreds forms and 500+ fields in each study

SDTM

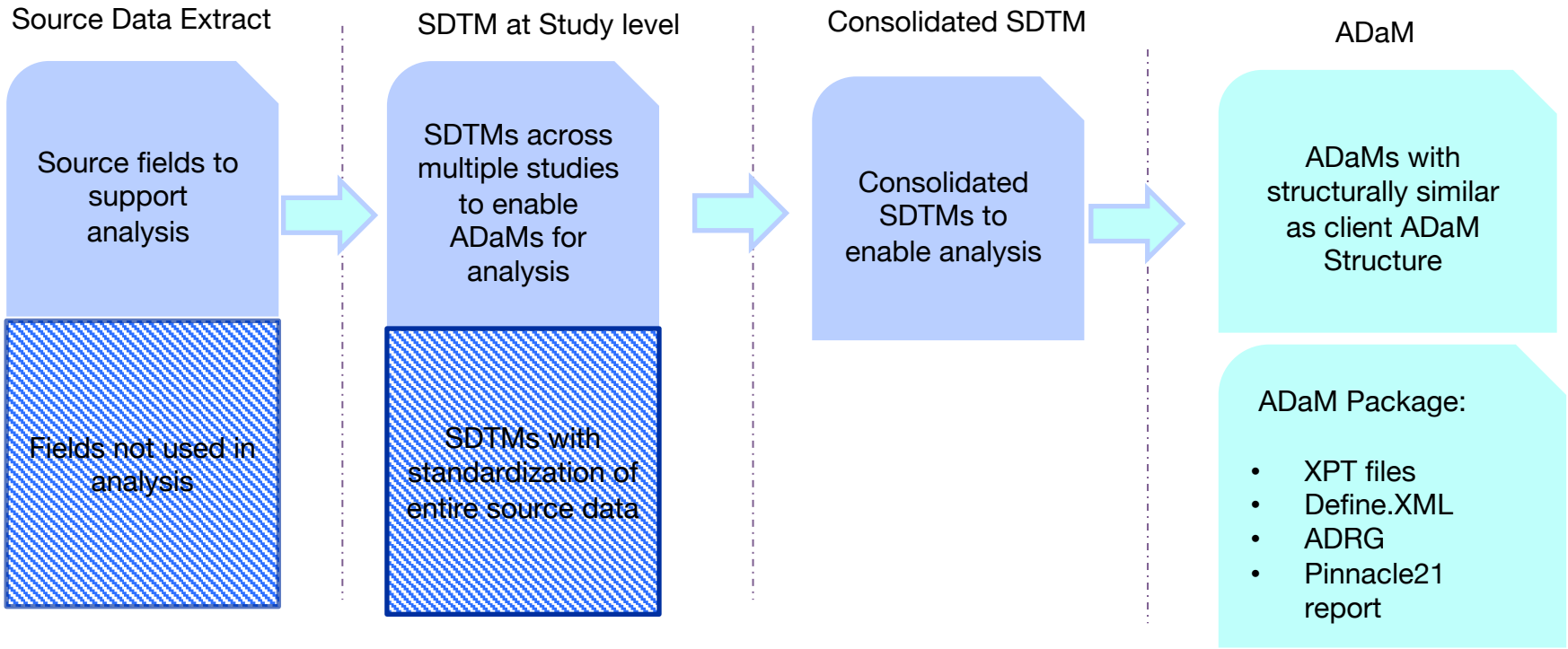
SDTMs for multiple Studies (~typically, 40 domains per study)

SDTM Submission Package

For each study:

- Database mapping
- Unique Field Reports
- SDTM Specification
- ~typically, 30 to 50 SDTM domain XPT files
- Define.XML
- SDRG
- Validation Report from Pinnacle21

Synthetic Control Arm – *Comparison Phase*



Synthetic Control Arm – *Models & Methods*

Simple mean, median or fixed-effect pooling	• Easy to perform. • Easy to interpret. • Requires high congruence between external and internal data. • Often only valid for restrictively small sub-group populations. Thus, falls short on precision.
Multivariate regression, propensity scoring	• Adjusts for imbalance to the extent explanatory factors are available in data. • Relatively easy to perform & interpret. • Generally considered valid with good data and sufficient plausible confounding variables. • Methods can be complex or relatively time consuming to implement and test. • Examples of applications with counter-intuitive findings exists, thus underscoring the need to have available and consider as many possible confounders as possible
Bayesian mixed-model commensurate power priors.	• Can restore patient balance and weigh the contribution of multiple sources of data adequately. • Difficult and complex to implement. • Often computationally heavy.
Random forests, Neural Networks, Cluster analysis (Gaussian mix	• Can identify homogeneous sources of data for enhanced validity. • Mostly exploratory in nature and requires separate statistical analysis to produce synthetic control. • No guarantee findings will be interpretable or useful for further analysis.

SCA Challenges

- Access to high quality data and awareness of SCA
- Does the original data collection process align with that of the current trial?
- Is the external control population sufficiently similar to the clinical trial population?
- Available data may not fit the needs of the current study
- Generalizability of results, interpretation and associated statistical methodology

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7218288/

Examples

Examples based on Approval

- 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]

Questions?

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