# *The Power of Sharing Clinical Data: Developing an External Control Arm for Registration*

**Mike.Litzsinger**@ProjectDataSphere.org

www.ProjectDataSphere.org

@ProjDataSphere

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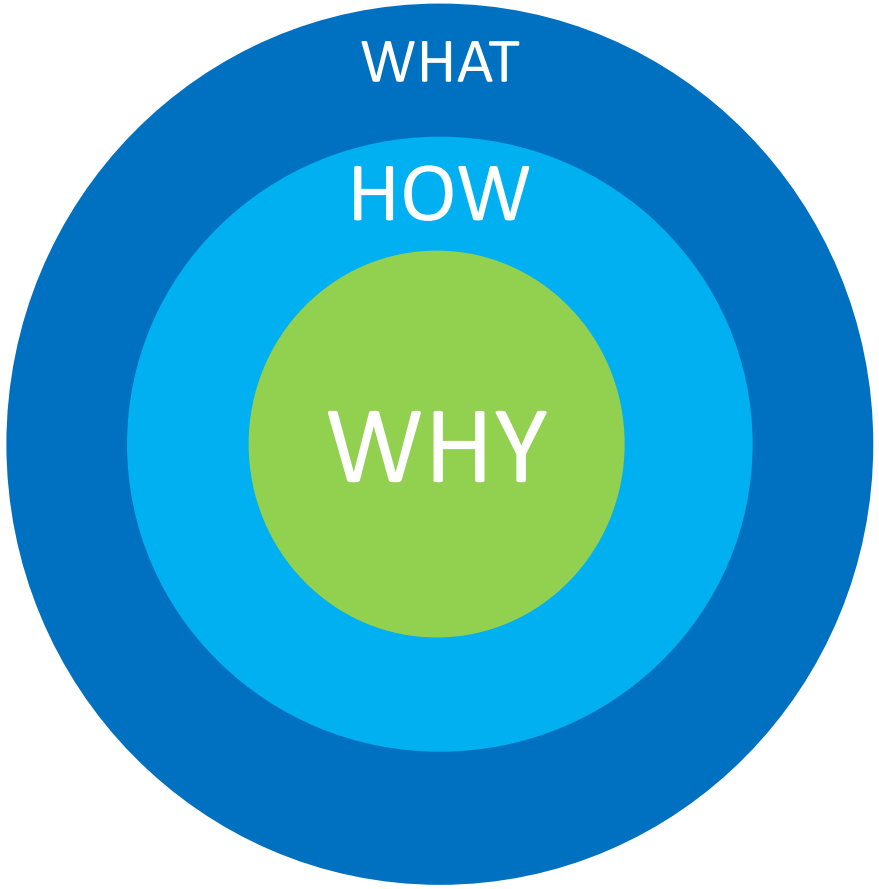
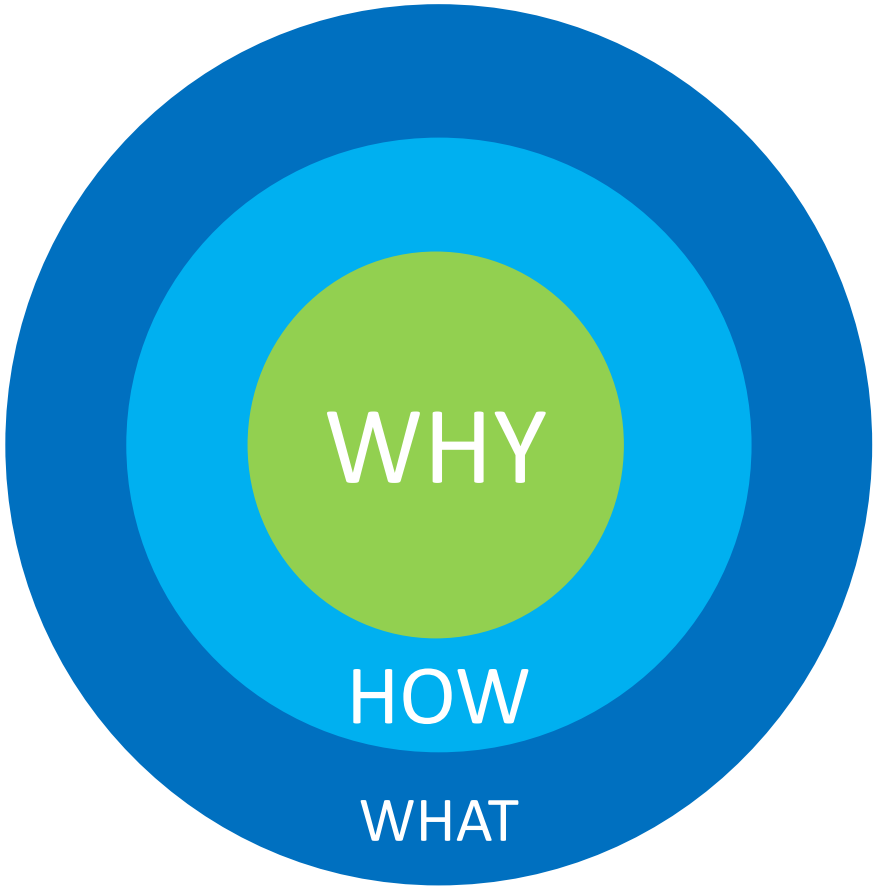
# Agenda

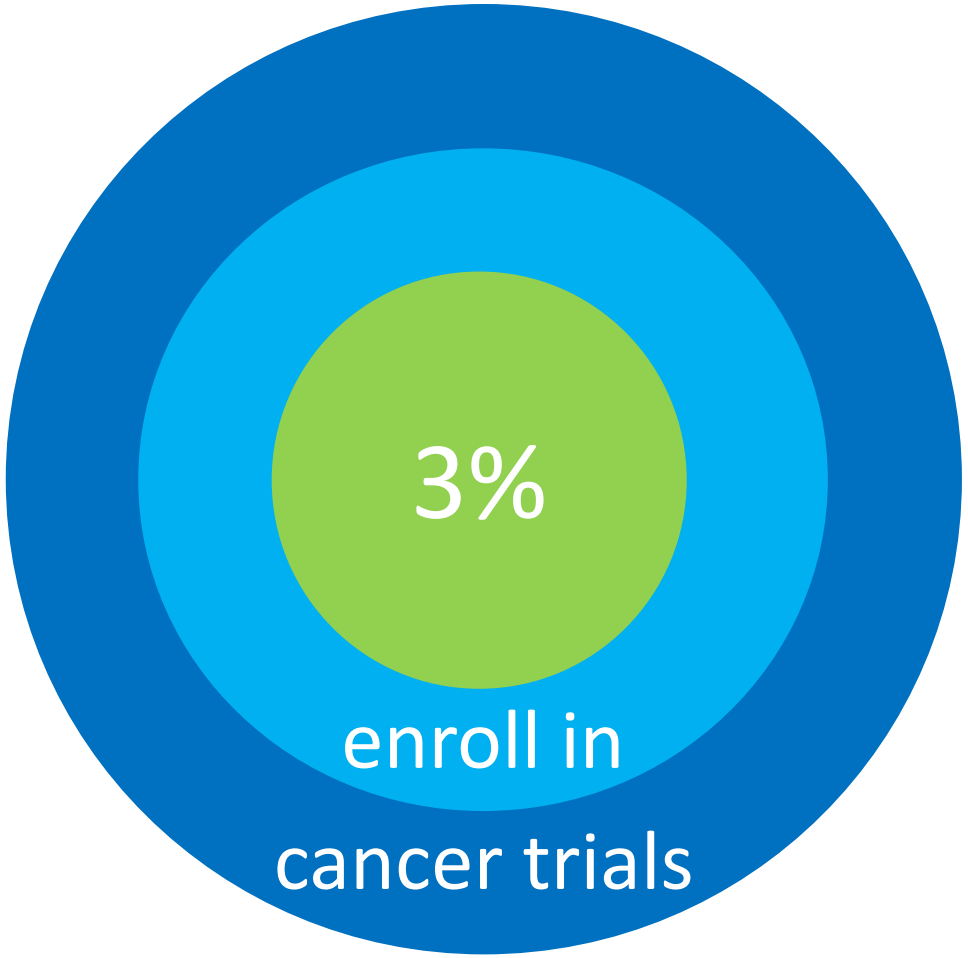
- WHY create an External Control Arm (ECA)?
- WHAT is an External Control Arm?
- Project Data Sphere® (PDS)
- PDS External Control Arm Research Program
- Insights from Version 1.0
- Glide Path for ECA Use in Registration
- Additional research

# Start With Why *[2009, Simon Sinek]*



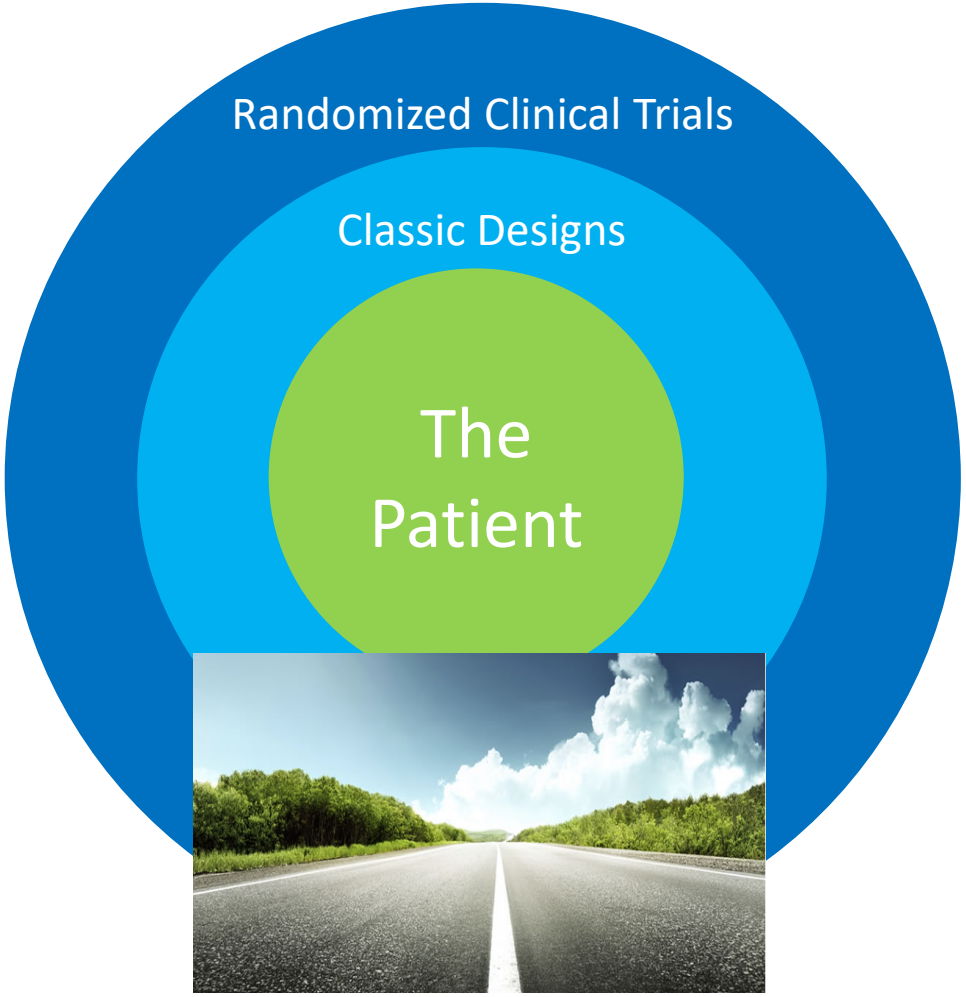



# Let's figure out the WHY




- Approximately 3% of adult cancer patients participate in clinical trials
- However, depending on the randomization, a substantial portion of those 3% are not assigned to experimental therapy
- Let's make those PATIENTS the WHY

# Start with the PATIENT

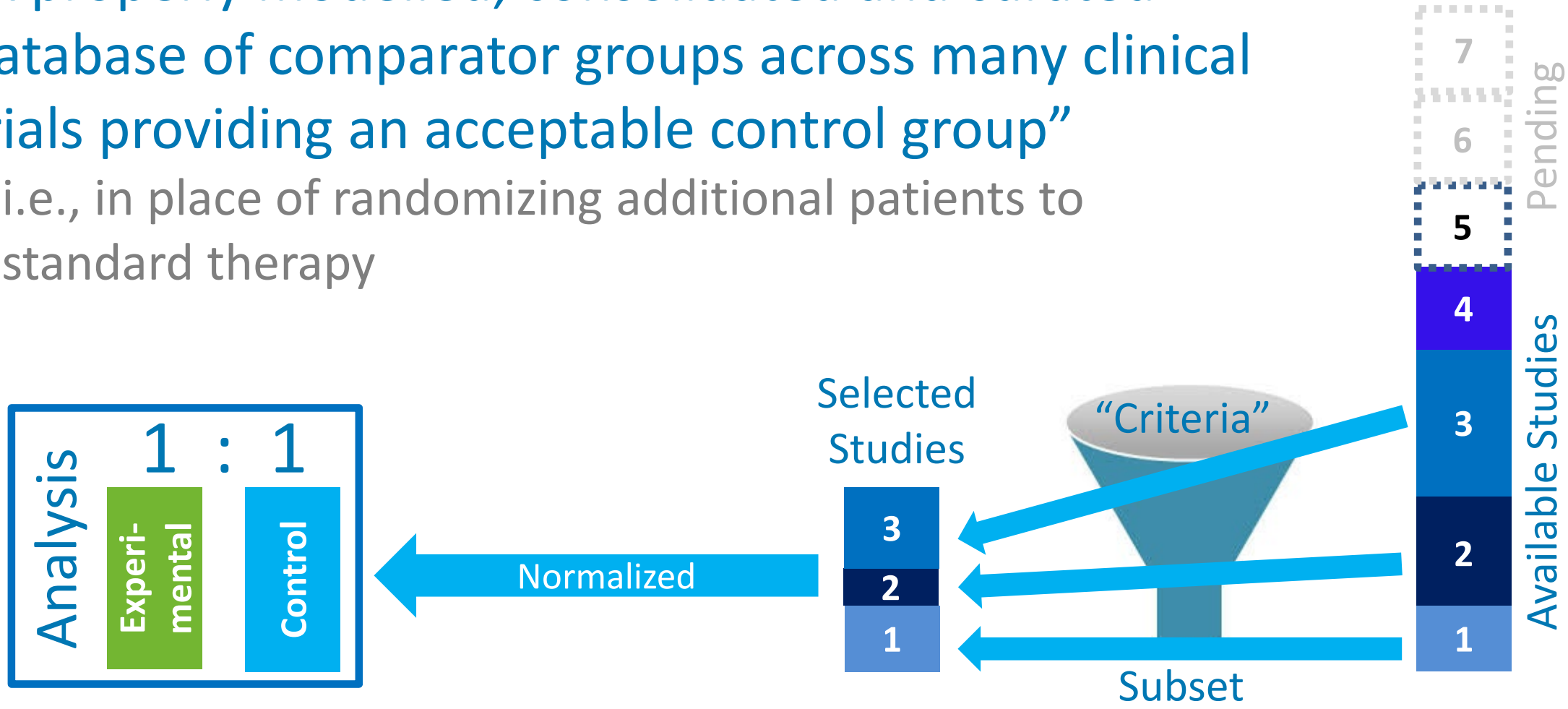



**Innovative Trial Design Pathway**

- We keep traditional methods …
- … and build …
- … an innovation pathway
- We embrace innovative designs and establish appropriate controls to benefit PATIENT CHOICE

# What is an External Control Arm (ECA)?

- "A properly modelled, consolidated and curated database of comparator groups across many clinical trials providing an acceptable control group"
  - i.e., in place of randomizing additional patients to standard therapy



# What is an External Control Arm? (continued)

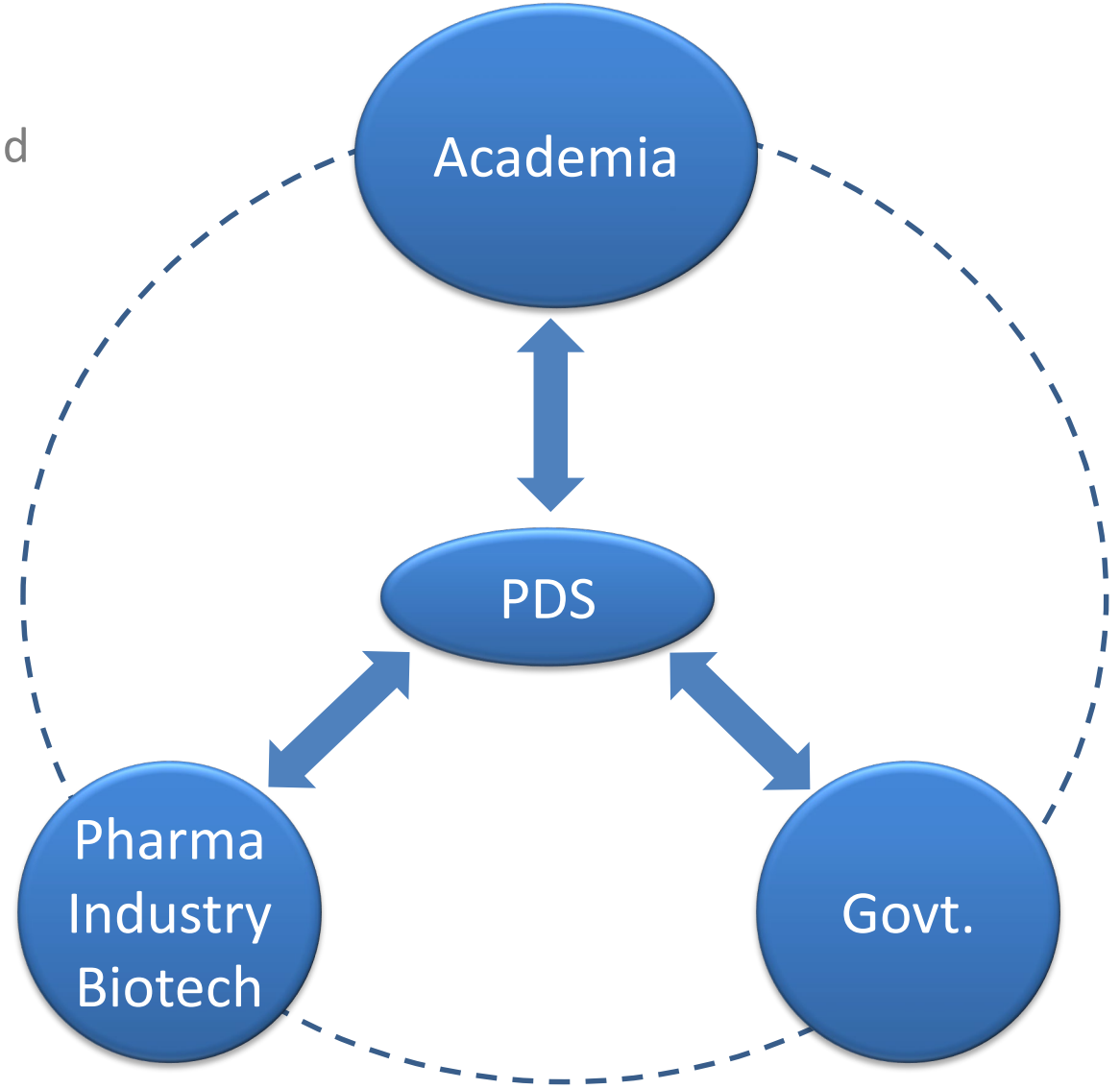
- **Advantages:**
  - Far fewer patients would need to be enrolled
  - Enrollment costs and timelines would be reduced
  - Would incentivize patients because they are more certain to receive experimental therapy
  - Prepares a standard therapy pool for testing trial designs
- **Disadvantage:**
  - *"The externally controlled study cannot be blinded and is subject to patient, observer, and analyst bias"* (*Guidance For Industry E10 Choice of Control Group and Related Issues in Clinical Trials*, May 2001)
- **What success looks like:**
  - Use of an External Control Arm to directly support new drug registration with a regulatory authority

# Project Data Sphere®: *Brief History*

- Launched 8Apr2014
- **Mission:** Broadly share, integrate, and analyze industry and National Cancer Institute Phase II and III de-identified clinical trial cancer data
- **Strong FDA engagement**, including co-sponsorship of recurring *FDA-PDS Symposia*
- **4 ongoing research programs**, including the *External Control Arm* program
- **Progress to date**: *27 peer-accepted* publications resulting in growing platform use

# Project Data Sphere: *Role*

- **Convener**
  - Brings together experts from academia, industry, and regulatory agencies
  - Organizes taskforces, workshops, and symposia
- **Collaborator**
  - Conceives novel research questions
  - Executes research initiatives
- **Catalyst**
  - Aggregates DATA to accelerate cancer research
  - Creates enriched datasets
- **Challenges**
  - Removing barriers to sharing data
  - Enabling interoperability of data sharing platforms



# External Control Arm Research Program: *Background*

- **Inspired and developed in partnership with FDA *Oncology Center of Excellence***

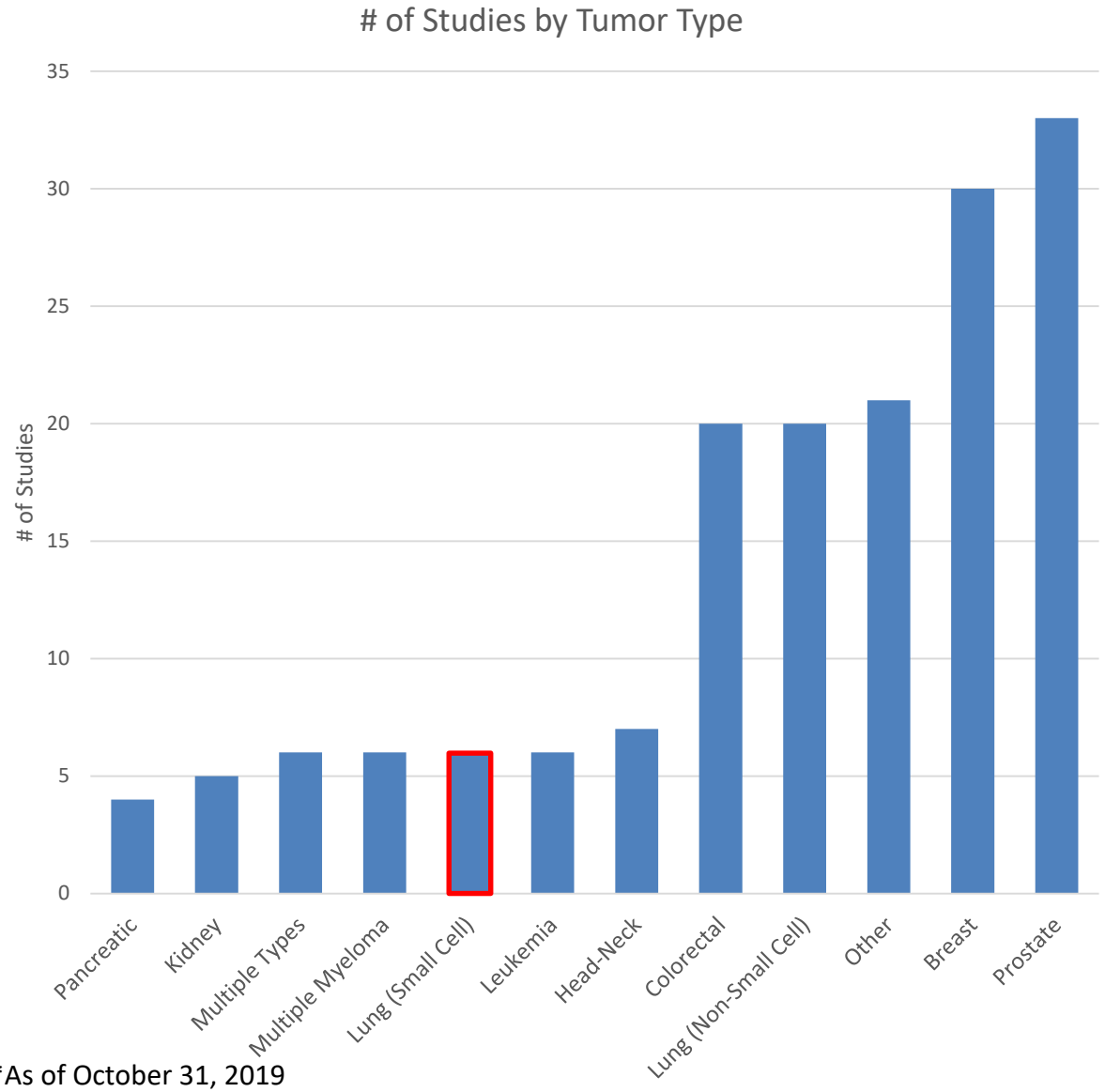
- ***FDA-PDS Symposium VI*: *Small Cell Lung Cancer* (SCLC) *"External Control Arm":***
  *A Paradigm Shift in Cancer Drug Evaluation/Registration* (August 2018)
  - >60 oncologists, data scientists, industry **leaders and regulators participated**
  - **Unanimous support** for building external control arm on **Etoposide + Platinum** as this had been the standard therapy for two decades
  - ***Letter of Support*** from FDA *Oncology Center of Excellence* signed by Dr. Richard Pazdur, 4Jan2019

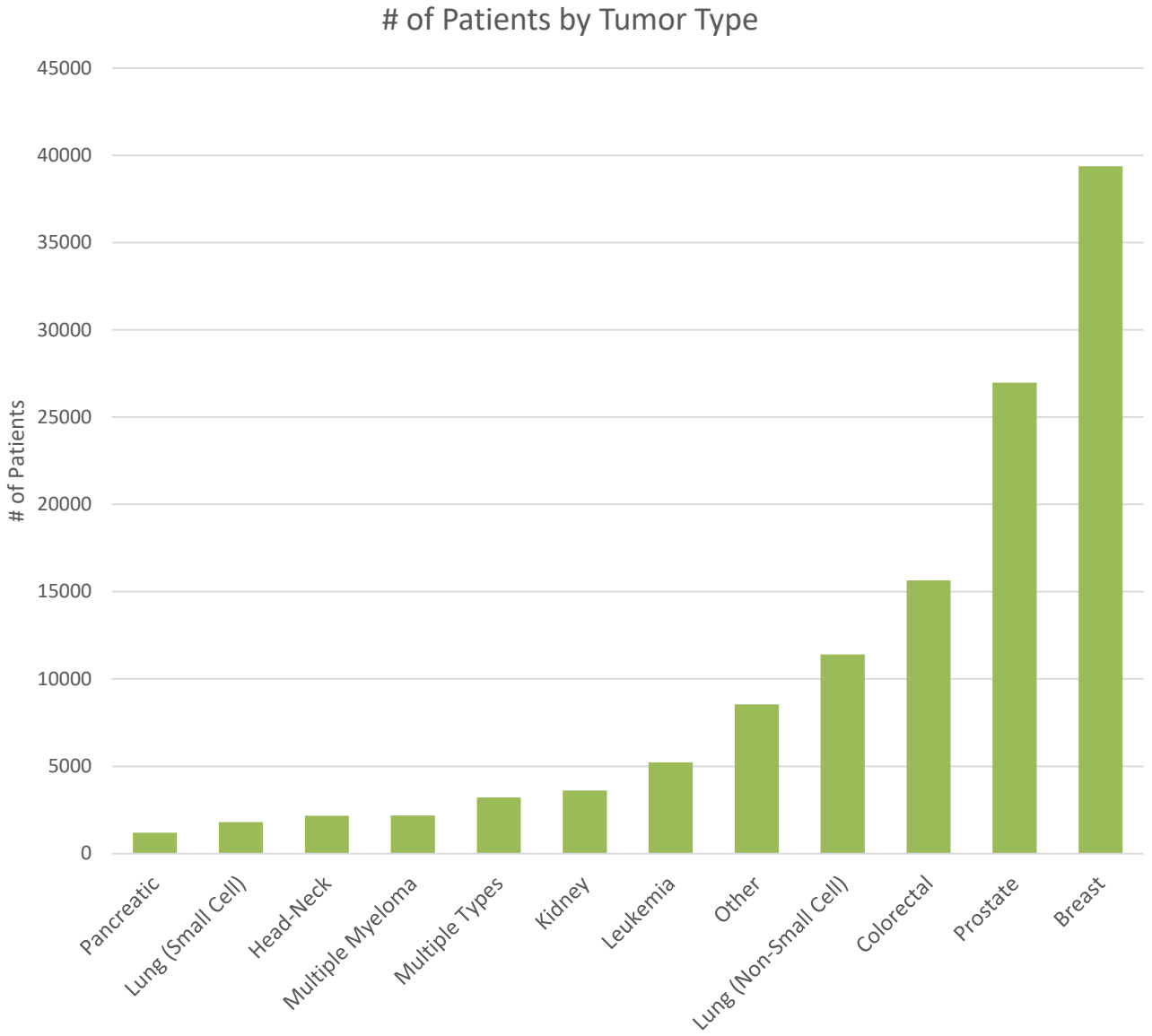
- **Research Program Goal**: Develop *SCLC External Control Arm* as an alternative to randomizing patients to standard therapy comparator arms for SCLC trials, with sufficient robustness to support regulatory decision-making
  - **Develop methods that produce *statistically persuasive*** results for a range of tumor types where the standard therapy has been unchanged over a long period of time
  - An experienced team from ***Dana-Farber Cancer Institute*** developed PDS SCLC ECA Version 1.0

# ECA Program Milestones: *Accomplishments*

- **Summarized impactful variables** known to be related to overall survival in SCLC
- **Identified, requested 30 clinical studies** using **Etoposide + Platinum** as control
- **Received 6 SCLC datasets to date** (of up to 20 expected) and loaded onto PDS platform
- Made progress with first 5 SCLC datasets
  - Assessed for sufficient power to support ECA
  - Normalized and aggregated for analysis
  - Developed initial external control arm
- **Authored "Methods" paper** describing SCLC ECA data and statistical processes
  - Curated dataset is ready to be loaded onto PDS Platform

# PDS Platform: 24 Tumor Types, >100,000 Patient Lives




*As of October 31, 2019

# *Prognostic Factors* Across 5 PDS SCLC Datasets

| Study | NCT.0000.3299 | NCT.0036.3415 | NCT.0011.9613 | NCT.0143.9568 | NCT.0045.3154 |
|---|---|---|---|---|---|
| **Demographic Variables** | | | | | |
| Age | Yes | Yes | Yes | Yes | Yes (<=or > 65) |
| Sex | Yes | Yes | Yes | Yes | Yes |
| ECOG Performance Status | Yes | Yes | Yes | No | Yes |
| Smoking before the study | No | No | No | Yes | No |
| Metastases present at enrollment | Yes | No | No | Yes | No |
| Prior surgery before study | No | No | Yes | Yes | No |
| Weight loss within last 6 months | No | No | No | No | No |
| **Genomic and Clinical Variables** | | | | | |
| Baseline Hemoglobin level | No | Yes | Yes | Yes | No |
| Baseline LDH in normal range | No | Yes | Yes | No | No |
| HER2 | No | No | No | No | No |
| CYFRA 21-1 | No | No | No | No | No |
| TP53 | No | No | No | No | No |

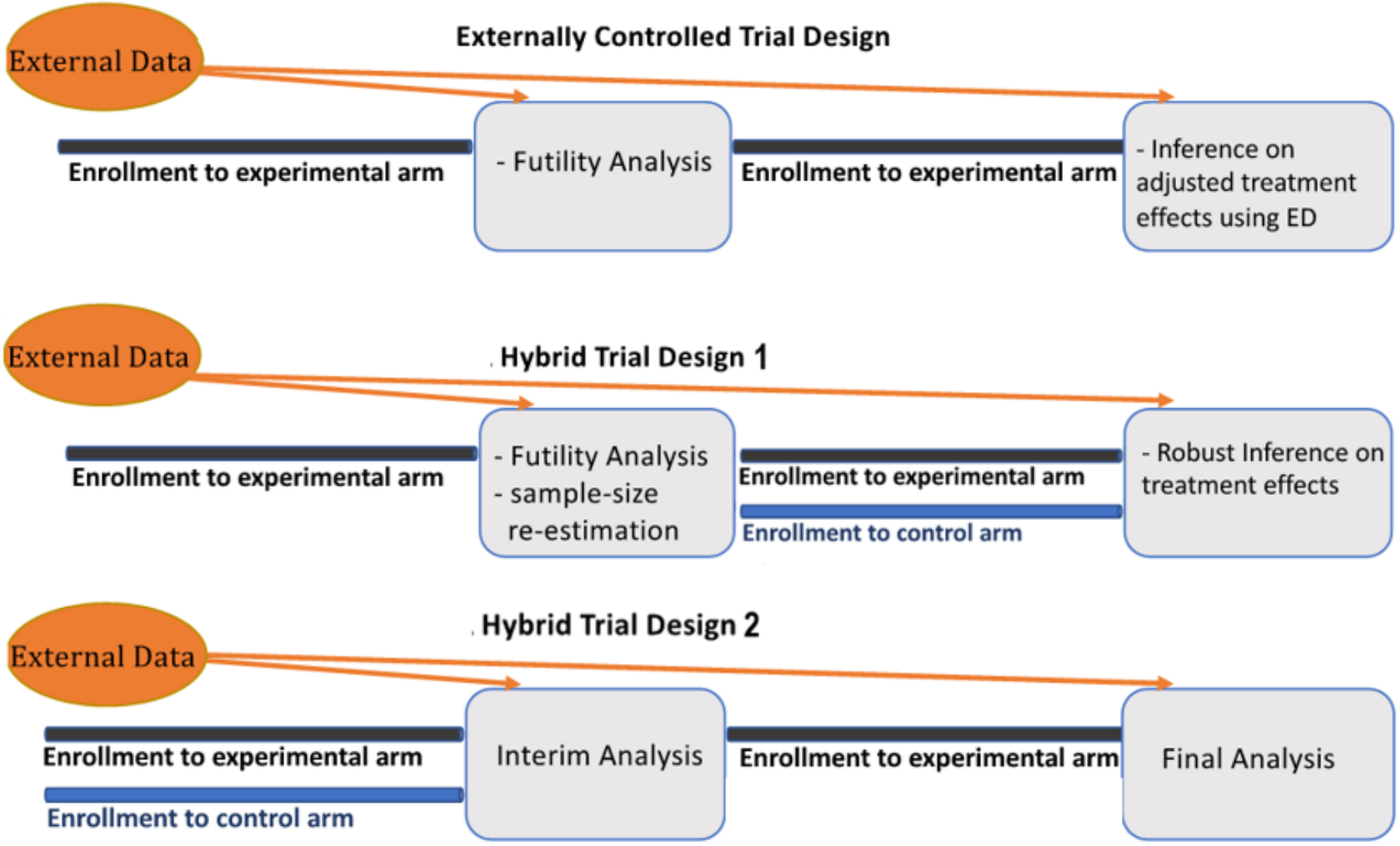
# *Patient Characteristics* Across 5 PDS SCLC Datasets

| Study | Total | NCT.0000.3299 | NCT.0036.3415 | NCT.0011.9613 | NCT.0143.9568 | NCT.0045.3154 |
|---|---|---|---|---|---|---|
| Enrollments | 1,053 | 283 | 455 | 232 | 42 | 41 |
| Trial Start Year | | 1998 | 2006 | 2002 | 2011 | 2007 |
| Sex * | | | | | | |
| Male | 656 (62) | 130 (46) | 330 (73) | 159 (69) | 17 (40) | 20 (49) |
| Female | 397 (38) | 153 (54) | 125 (27) | 73 (31) | 25 (60) | 21 (51) |
| Age * | | | | | | |
| <65 | 398 (38) | 96 (34) | 180 (40) | 80 (34) | 26 (62) | 16 (39) |
| ≥65 | 655 (62) | 187 (66) | 275 (60) | 152 (66) | 16 (38) | 25 (61) |
| Race | | | | | | |
| White | 945 (90) | 255 (90) | 379 (83) | 232 (100) | 39 (93) | 40 (98) |
| Black | 28 (3) | 17 (6) | 8 (2) | - | 2 (5) | 1 (2) |
| Indian/Alaskan | 2 (0) | 2 (1) | - | - | - | - |
| Asian | 62 (6) | 1 (0) | 61 (13) | - | - | - |
| Other | 16 (2) | 8 (3) | 7 (2) | - | 1 (2) | - |
| ECOG PS * | | | | | | |
| 0 | 218 (21) | 80 (28) | 121 (27) | - | - | 17 (41) |
| 1 | 662 (63) | 189 (67) | 277 (61) | 181 (78) | - | 15 (37) |
| 2 | 128 (12) | 13 (5) | 55 (12) | 51 (22) | - | 9 (22) |
| Missing | 45 (4) | 1 (0) | 2 (0) | - | 42 (100) | - |

# Version 1.0 Methodology Insights (Part 1)

- Unlike randomized controls, external controls have some risk of bias.
- Version 1.0 methodology reduces bias by adjusting confounding variables, and estimates the residual bias (and inflation of type 1 error) through simulations.
  - Select a completed trial with an unbiased treatment effect, and isolate it as a single arm trial using the experimental data.
  - If treatment effect is different, randomization is necessary.
  - If treatment effect is the same, randomization not needed.
- Residual bias can be further reduced through hybrid experimental designs.

# Designs to Consider



# Version 1.0 Methodology Insights (Part 2)

- Judging whether the method is statistically compelling is difficult out of context of the experimental treatment – Is the effect size sufficient to accept the estimated bias and estimated inflation of type 1 error?
- Version 1.0 methodology was statistically persuasive in addressing bias and is successful to reduce the number of clinical trial patients randomized to standard therapy.
- Applied methods are applicable to other tumor types with a same limited change over time in standard therapy.
- Capturing more data attributes (e.g., quantitative tumor progression, which correlates to Overall Survival) would additionally strengthen the Version 1.0 methodology.

# Glide Path for ECA Use in Registration

- **Community development**
  - FDA asks that new pathways to approvals (such as ECAs) to be driven and nurtured by the community and then to be presented back to them
  - It is doubtful that they will proscribe specific criteria for ECAs beforehand
  - FDA is looking at these efforts to educate them on how to react when ECAs are part of submissions
- **Sponsors to engage and consider innovative trial designs during Phase I and II**
  - Plan path to use an ECA and methodology for internal assessment and/or for registration
  - End of Phase 2 could be a very instructive time for sponsor internal decisions, regulatory discussions
- **Share within the communities**
  - Make Version 1.0 dataset and methodology available on PDS platform
  - Promote use cases!
- **Is there opportunity for more systematic compilation of control arm data? Yes!**
  - Submit control arm data on reigning standard therapy via a neutral pathway (like PDS)

# Additional ECA Research: NSCLC

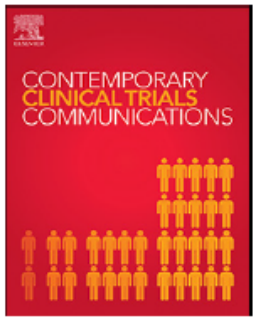
- A Canadian research team published an independent approach in Sep 2019:

ELSEVIER

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc




Research paper

## Minimizing control group allocation in randomized trials using dynamic borrowing of external control data – An application to second line therapy for non-small cell lung cancer

Louis Dron[a,c,1], Shirin Golchi[b,c,1], Grace Hsu[b,c], Kristian Thorlund[a,c,*]

[a] *Department of Health Research Methodology, Evidence, and Impact, McMaster University, Hamilton, ON, Canada*
[b] *Department of Statistics and Actuarial Science, Simon Fraser University, Burnaby, BC, Canada*
[c] *MTEK Sciences, Vancouver, BC, Canada*

# Additional ECA Research: NSCLC (continued)

| Study | Total | NCT.0007.6388 | NCT.0031.2377 | NCT.0068.6959 | NCT.0036.4351 |
|---|---|---|---|---|---|
| Enrollments | 4662 | 1433 | 1391 | 598 | 1240 |
| Trial Start Year | | 2004 | 2006 | 2008 | 2006 |

- **4 NSCLC datasets on PDS platform were assessed, standardized and aggregated to develop an additional ECA**
- **Authored and published "Methods" paper** describing data and statistical processes associated with NSCLC ECA:
  - Researchers noted that ***"…applied examples utilizing external control data are sparse".***
  - And "*we therefore illustrate how Bayesian dynamic borrowing of external individual patient level control data from similar clinical trials can often reduce randomization to the control intervention without substantially trading-off precision".*

# Comments and discussion

***Thank you!***

Mike.Litzsinger@ProjectDataSphere.org

www.ProjectDataSphere.org

@ProjDataSphere