An Alternative to "*Traditional*" Master Protocols to Progress a Pipeline of Therapies for Cystic Fibrosis

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THERAPEUTICS
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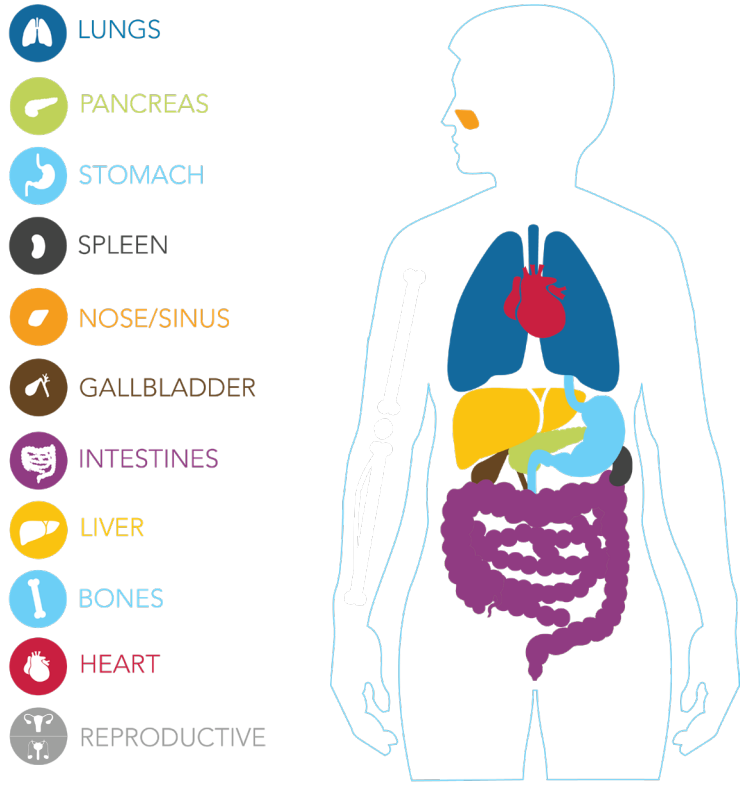
Cystic fibrosis (CF)

- Life-shortening, multi-organ genetic disease
- People living with CF carry two “disease-causing” variants of the *CFTR* (CF transmembrane conductance regulator) gene
  - Approximately 39,000 living with CF in the US and 105K diagnosed worldwide*
- Recent regulatory approvals of CFTR targeted therapies have significantly changed the landscape of CF clinical care through dramatic improvement of CF co-morbidities

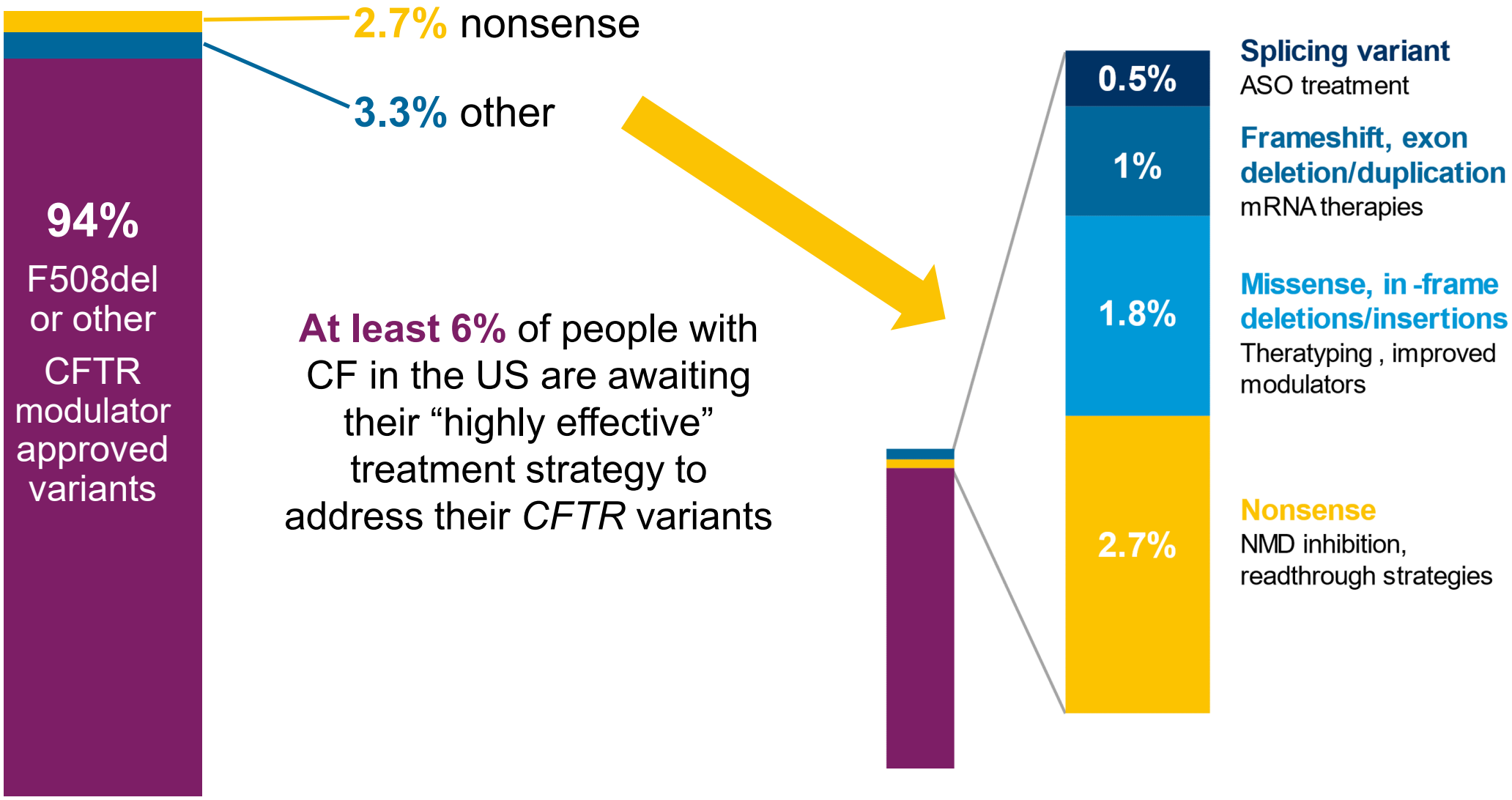


CFTR Modulators: Systemic small molecule therapies that increase CFTR function

2021 Annual Data Report. Bethesda, Maryland. ©2022 CFF
*Cromwell et. al. Journal of Cystic Fibrosis 22 (2023) 436–442
*Guo et. al. Journal of Cystic Fibrosis 21 (2022) 456–462

Modulator Ineligible Population: An Ultra-Rare, Heterogenous Sub-Population

Nucleic acid-based therapy approach will be needed to provide CFTR function



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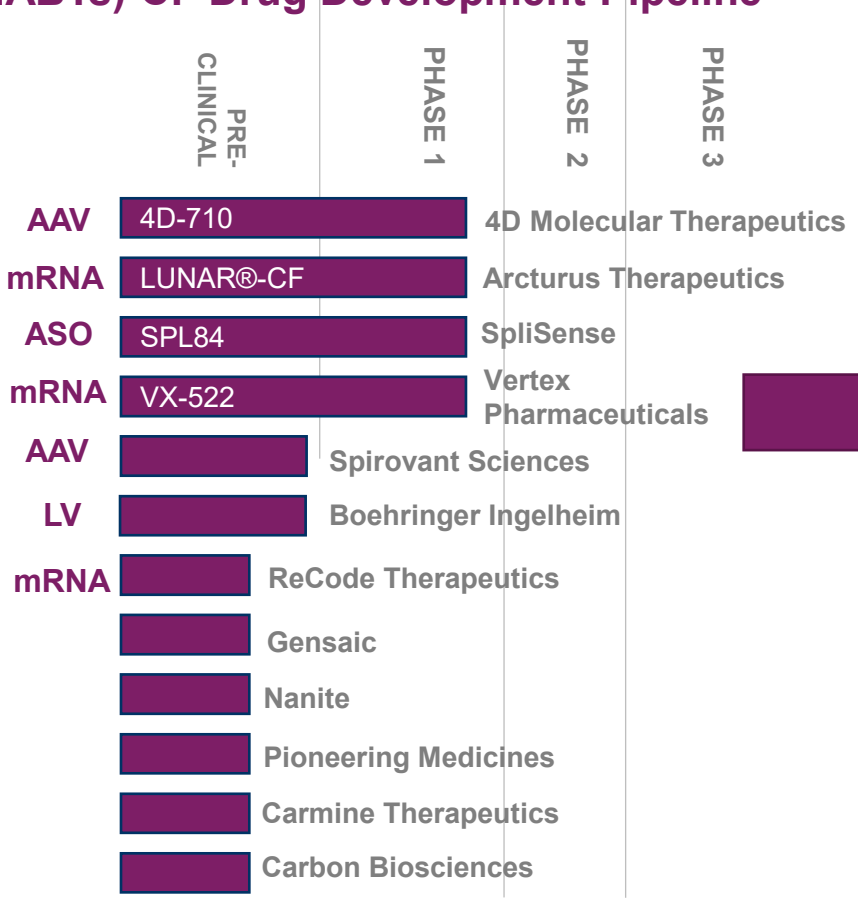
Nucleic Acid Based Therapies* (NABTs) CF Drug Development Pipeline



*NABTs include ASOs, mRNA, viral-vector based (e.g.: AAV, lentivirus, herpes virus) gene delivery therapies

https://apps.cff.org/trials/pipeline/ for current

~1100

adults with CF ineligible for modulators

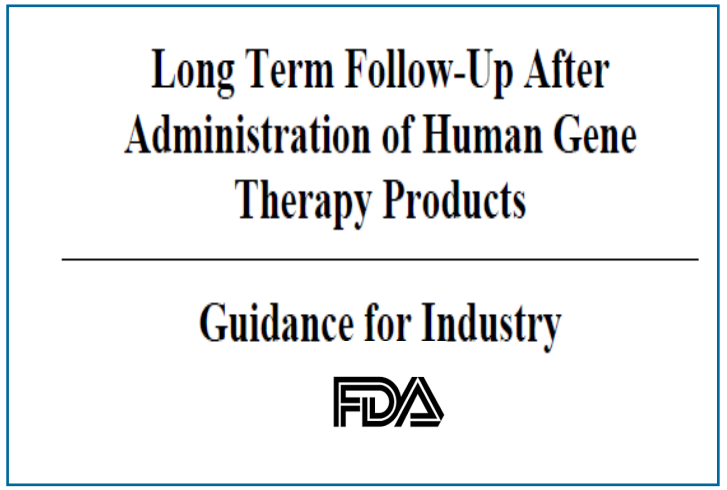
& ppFEV$_1$ 40% & no lung transplant

~25% are BIPOC and/or Hispanic

<25% with prior research trial experience

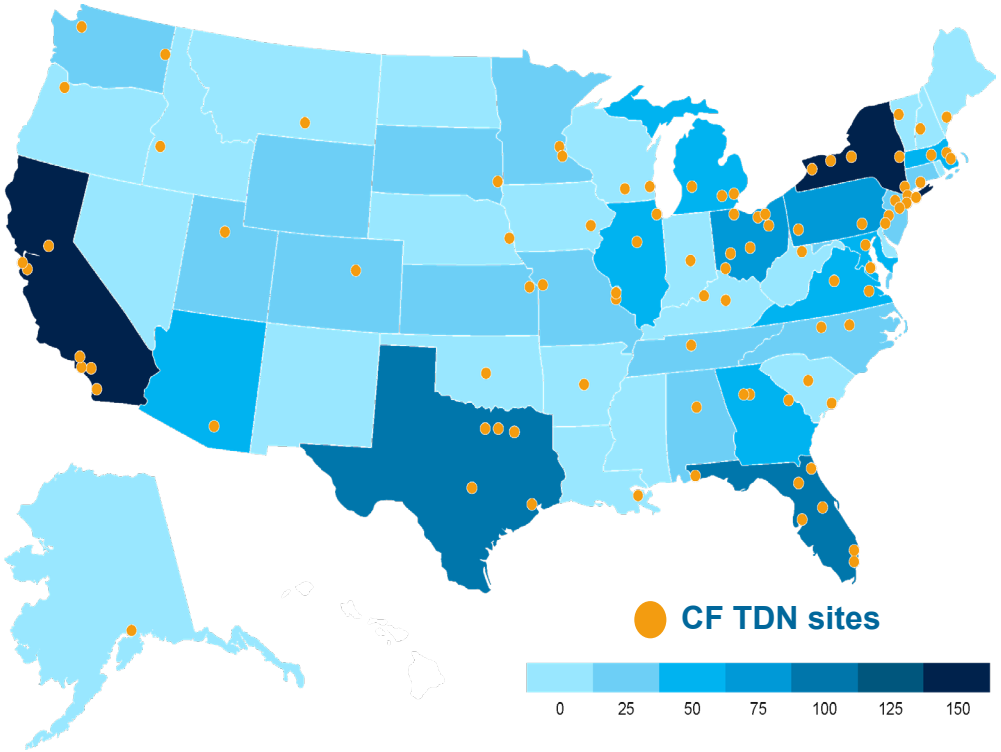
Additional Risk of a Diminishing Participant Pool over Time

- Sponsors hesitant to include trial participants who received prior NABT therapy
  - Some (but not all) therapies (e.g. lentiviral based gene therapies) are "one shot" independent of therapeutic benefit
- Regulatory required **long term safety studies,** *regardless of therapeutic benefit and study phase*, are anticipated to complicate participation in competing ongoing investigational trials
  - Co-enrollment generally not allowed by competing sponsors



CF Therapeutics Development Network (TDN): Uniquely Positioned to Advance the Pipeline

Number of Adults with CF Not Eligible for Modulators



- Largest CF clinical trial network comprised of 91 CF trial centers across the U.S.
  - **16 FDA-approved therapies since 1998**
- Scientific review and sanctioning process for all industry sponsored trials
- Extensive patient education and referral programs to connect people with CF to trial sites
- Standardized research procedures and a centralized DSMB
- Established partnerships with CF community stakeholders and global clinical trial networks

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Master Protocols...
to Efficiently Progress a Pipeline of NABTs?

~1100 Modulator Ineligible adults with stable disease in the U.S., ~<25% (275) with prior trial experience

***Potential* NABT Trials for PwCF Ineligible (Intolerant) for Modulators**

Variant *Specific*

ASO Therapy A

Variant *Agnostic*

mRNA Therapy B

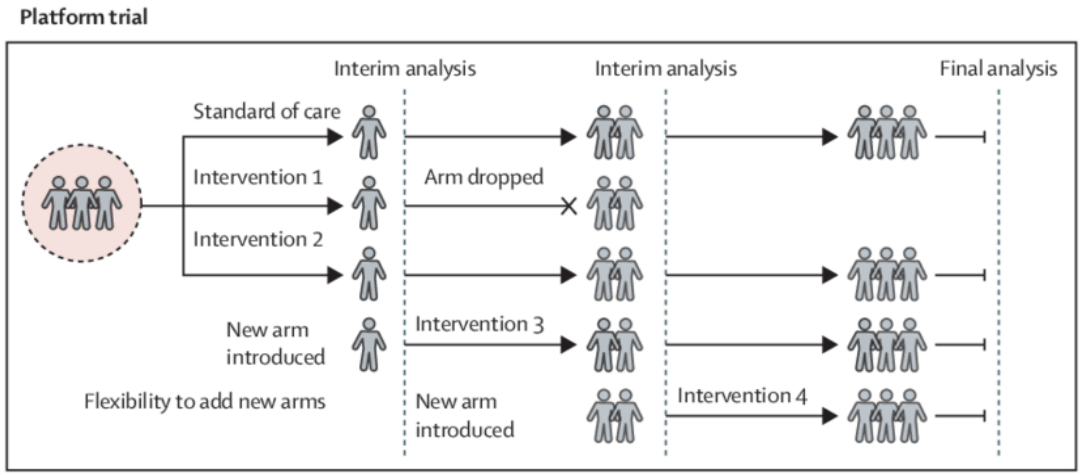
mRNA Therapy C

Viral Vector Gene Therapy D

FDA Center for Drug Evaluation and Research

FDA Center for Biologics Evaluation and Research

Long Term Safety Follow-up Studies



Advantages… *assuming alignment can be achieved for a therapeutic protocol*:

- Potential to add and adaptively drop arms to optimize limited patient resources
- Shared control arm to reduce trial sizes across the pipeline
- Shared recruitment and trial implementation infrastructure
- Aligned oversight (steering committee, DSMB)

Image adapted from Mayer-Hamblett et. al. 2023 *Lancet Respir Med*
Image adapted from: Park, Jay & Ford, Nathan & Xavier, Denis & Ashorn, Per & Grais, Rebecca & Bhutta, Zulfiqar & Goossens, Herman & Thorlund, Kristian & Socías, María & Mills, Edward. (2021). Randomised trials at the level of the individual. The Lancet Global Health. 9. e691-e700. 10.1016/S2214-109X(20)30540-4.

Master Protocols...
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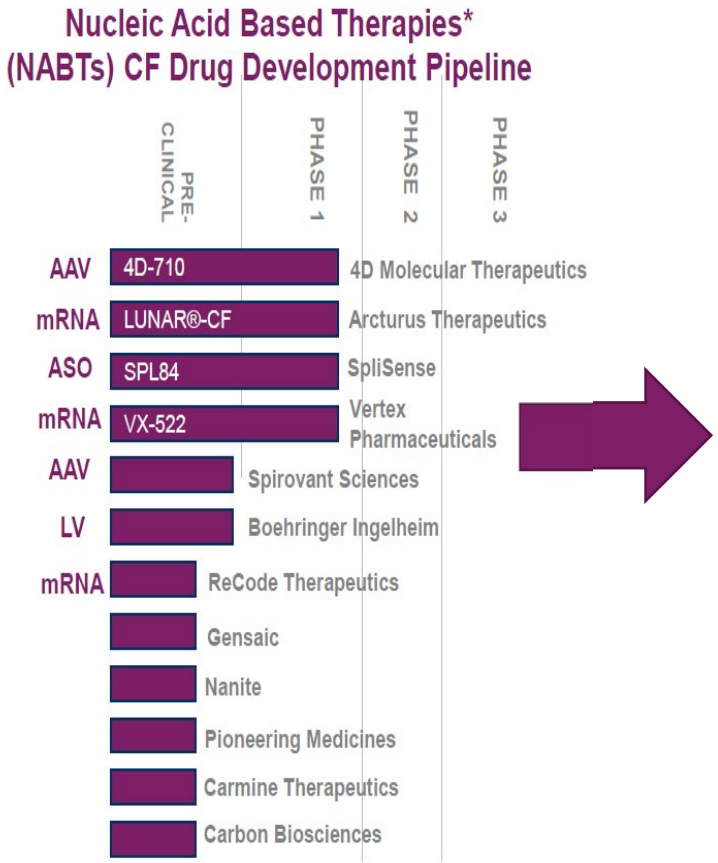


Select Key Challenges

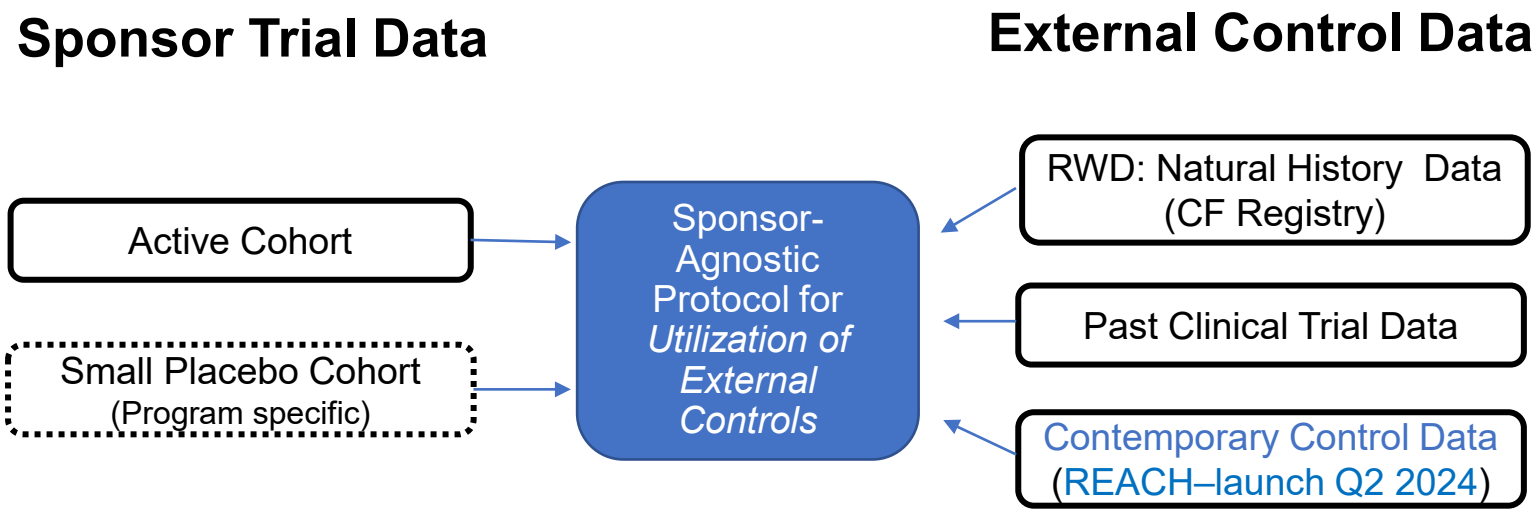
- Master protocol "ownership" is difficult if not impossible as a patient organization
  - Complex coordination of required INDs for each NABT
  - Inability to mandate sponsor participation
- Lack of agility for frequent trial adaptions in response to safety, etc
- Our ability to randomize to *any* active therapy arm is not necessarily acceptable or practical
  - Different risk-benefit profiles (e.g., lentivirus vs. mRNA), with variant-specific and agnostic approaches for consideration
  - Inability to offer all therapies at each trial site due to complexity and resourcing

One major advantage to a master protocol approach is a **shared control group** to support efficacy and safety assessments for trials likely to be using fewer (*or no*) placebo participants

Alternative Patient Organization-Trial Network Strategy:
Develop a sponsor-agnostic contemporary control "arm" for use across multiple sponsor driven programs

Sponsor Agnostic Master "External Control" Protocol

External Controls May Play *Either* a Primary or a Supportive Role for Regulatory Packages (Program Specific)



Research Expansion to Advance the CF THerapeutic Pipeline for People with CF without Modulators: (REACH) Study (***CF Foundation Sponsored, PI: D. Polineni***)

- **-Outcome data includes standardized NABT trial outcomes and time points of key interest**
- **-Standardized comparative safety data collection**
- **-Onsite monitoring of study data, use of regulatory compliant data systems**
- **-Conducted in the same trial network (TDN) as the NABT trials**

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"Being able to substitute the data you have with REACH participants; I think that's groundbreaking."

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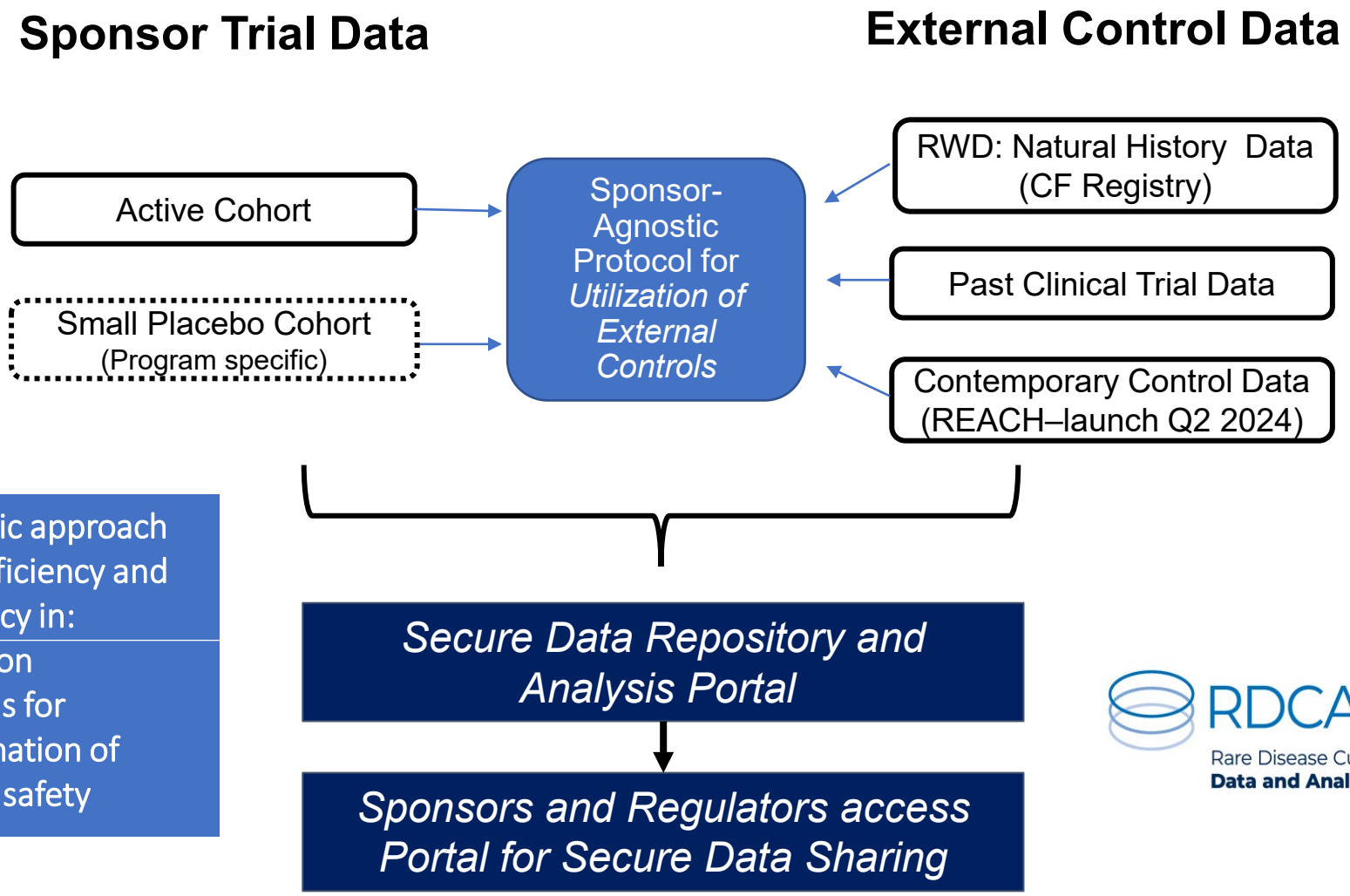

Sponsor-agnostic approach aims to build efficiency and consistency in:

- Data qualification
- Robust methods for unbiased estimation of efficacy and/or safety

RDCA-DAP® Rare Disease Cures Accelerator Data and Analytics Platform

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Where the Rubber Meets the Road
….An Opportunity for Increased Regulatory Collaboration

- Patient organizations and rare disease clinical trial networks are in a unique position to contribute to innovative trial design and clinical development planning
  - Designs which optimize a limited participant pool to maximize therapeutic “shots on goal”
- General desire from agency to pursue sponsor-specific interactions to discuss these trial design approaches
  - At the discretion of the sponsor
  - Confidentiality limits utilizing learnings from such a meeting across the pipeline

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➢ Formal mechanisms are needed to seek input from regulators *in a sponsor-agnostic setting* to progress and promote innovative trial design strategy

- Potential for expansion of the Complex Innovative Trial Design program to stakeholders *beyond those holding an IND*
- Mechanisms for patient organizations to independently contribute to "universal" data and/or methods qualification in support of innovative designs