FOUNDATION FIGHTING BLINDNESS

CLINICAL CONSORTIUM

Regulatory Endpoints and Trial Design for IRDs (REDI) Working Group Ongoing Efforts

Rachel Huckfeldt

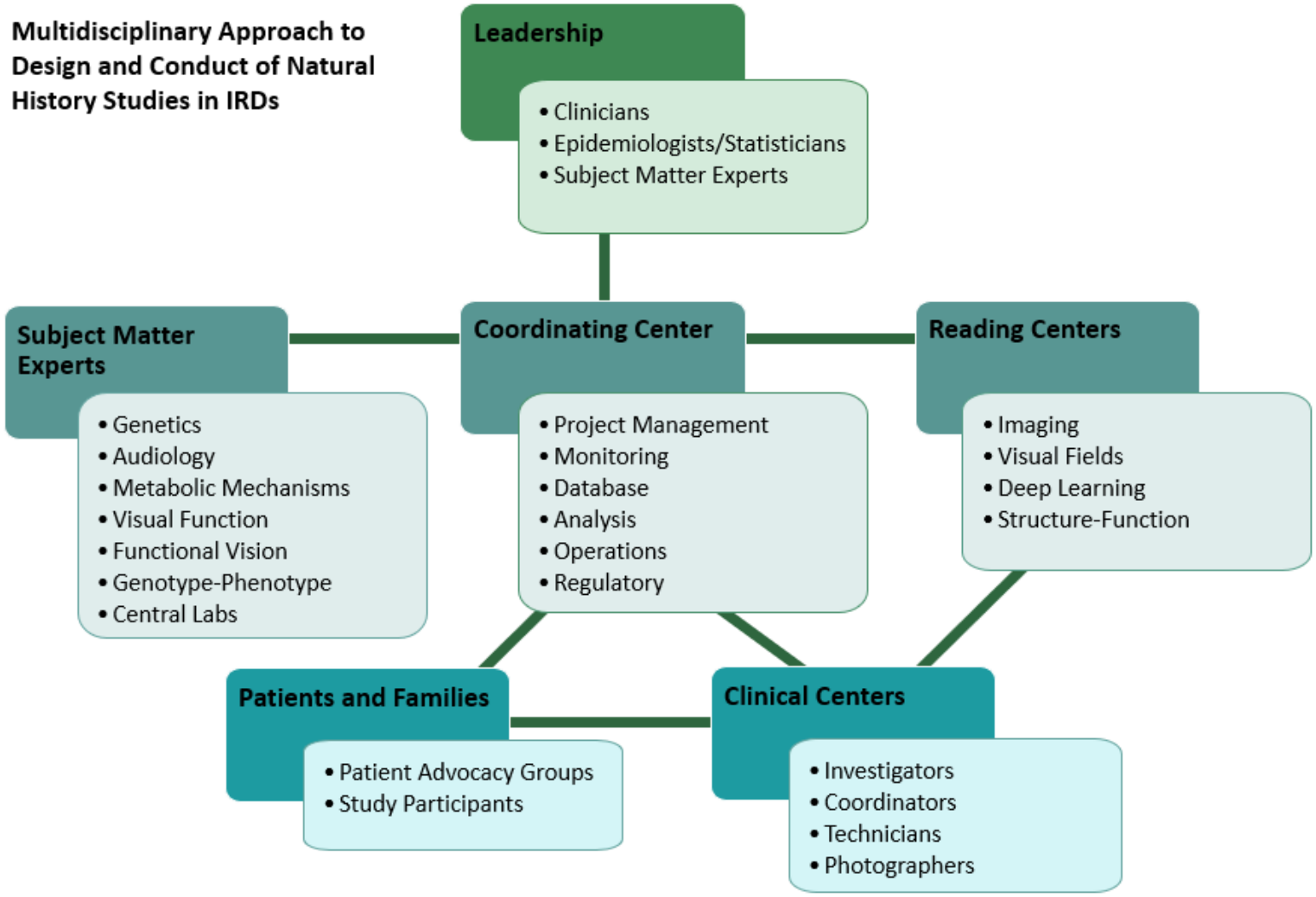
Disclosures and Funding

- **Presenter Disclosures**
  - Consultant: BlueRock Therapeutics, Janssen, Octant, Sanofi, Sepul Bio, SpliceBio, Sunovion
  - Research support: Ascidian, Beacon, Biogen, FFB, Janssen, MeiraGTx, NEI, Sepul Bio, Sparing Vision, SpliceBio
- **Funding provided by Foundation Fighting Blindness**

Consortium Overview

International consortium of clinical centers with expertise in inherited retinal degenerations (IRDs)

Goal: Accelerate development of treatments for IRDs



Ayala et al., The Importance of Natural History Studies in Inherited Retinal Diseases, Cold Spring Harbor Laboratory Press, 2023

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Natural History Studies

RUSH2A: Rate of Progression in *USH2A*-related Retinal Degeneration

Study Chair: Jacque Duncan, MD
Enrollment: 127 participants
Status: Year 4 visits completed in 2022; Year 7 and 9 extension underway

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Natural History Studies

RUSH2A: Rate of Progression in *USH2A*-related Retinal Degeneration	**Study Chair:** Jacque Duncan, MD **Enrollment:** 127 participants **Status:** Year 4 visits completed in 2022; Year 7 and 9 extension underway
Pro-EYS: Rate of Progression in *EYS*-related Retinal Degeneration	**Study Chair:** Mark Pennesi, MD, PhD **Enrollment:** 103 participants **Status:** Year 4 visits in 2025
RUSH1F: Rate of Progression of *PCDH15*-related Retinal Degeneration in Usher Syndrome 1F*	**Study Chair:** Katarina Stingl, MD **Enrollment:** 44 participants **Status:** Year 4 visits in 2027
GYROS: Gyrate Atrophy Ocular and Systemic Study†	**Study Co-Chairs:** Mandeep Singh, MD and David Valle, MD **Enrollment:** 45 participants **Status:** Year 4 visits in 2028
Uni-Rare: Universal Rare Gene Study‡	**Study Chair:** José Sahel, MD **Genes with natural history studies:** ***MYO7A*, *RDH12*, *CLRN1*,** multigene cohort **Status:** Year 4 visits in 2029

***Co-funded by FFB, Usher 1F Collaborative & Marjorie C. Adams Foundation**

†Co-funded by FFB, Conquering Gyrate Atrophy, and FDA – *This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award R01FD007628 totaling $1.6M with 46% funded by FDA/HHS and $1.9M and 54% funded by non-government source(s). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.*

‡Co-funded by Foundation Fighting Blindness, BlueRock Therapeutics, Opus Genetics, Atsena Therapeutics, Cove Therapeutics, Save Sight Now, Maryrose Sylvester, Anonymous Donor, Sarah de Coizart Trust, Max and Minnie Tomerlin Voelcker Fund, Usher III Initiative, Akouos.

Regulatory Endpoints and Trial Design for IRDs (REDI) Working Group

Mission: Collaborate with a wide range of subject matter experts to identify and propose best endpoints and study design methods for IRD clinical trials, obtain input from industry and regulatory representatives, and disseminate recommendations.

Endpoint Comparison Approach: Use Consortium NHS data to evaluate functional and structural measures of progression and compare **ideal properties** of candidate endpoints

- Large magnitude of change relative to variability in change (large "signal to noise")
- Change exceeds measurement variability (many eyes exceed "real" change)
- Sensitive to change in most of a population (lack of floor or ceiling effect)
- Relevant to how a patient feels or functions (clinically meaningful)

REDI Initiative #1: RUSH2A Endpoints

RUSH2A: Rate of Progression in *USH2A*-related Retinal Degeneration

- **Four-year prospective study with annual visits**
- **Study chair: Jacque Duncan, MD**
- **Eligibility criteria included:**
  - Clinical diagnosis of rod-cone degeneration (ARRP or USH2)
  - Biallelic *USH2A* variants
- **Primary cohort:**
  - ETDRS score ≥ 54 letters (Snellen equivalent 20/80; all participants ≥ 20/50)
  - Central visual field ≥ 10° diameter on kinetic perimetry

Assessments performed

- **Functional**
  - Visual acuity, static perimetry, microperimetry, full-field stimulus threshold testing, electroretinography
- **Structural**
  - Ellipsoid zone area on OCT
- **Patient-reported outcomes**
  - Visual function questionnaires (VALVVFQ-48 and MRDQ)

N=103 participants
with at least one follow-up visit

ARRP: Nonsyndromic autosomal recessive RP; USH2: Usher syndrome type 2

VA and EZ area have limitations as endpoints in *USH2A*-related IRD

Visual acuity

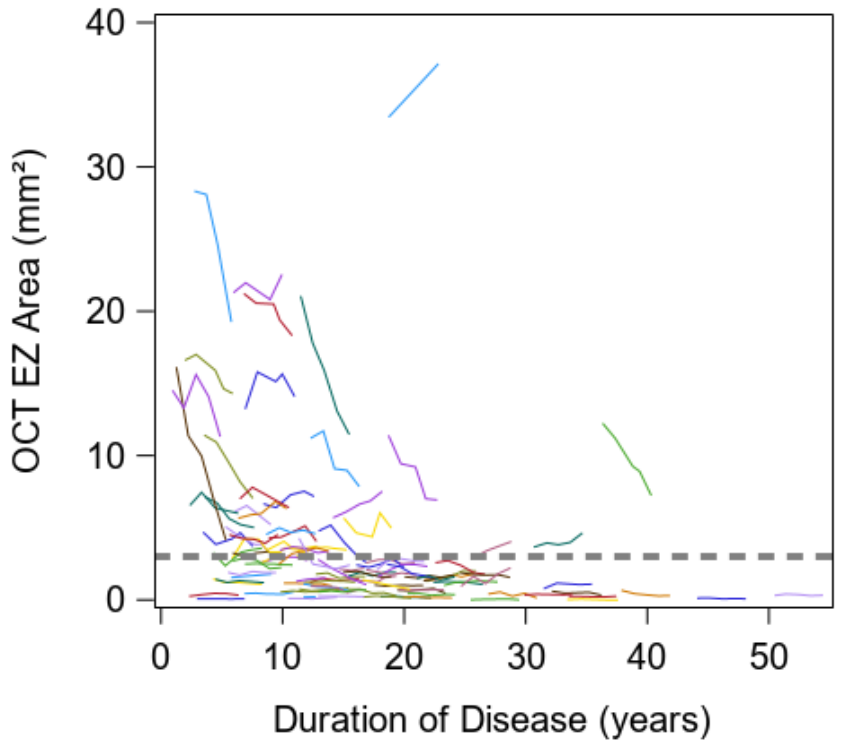
- Slow progression
  - Annual mean change ≤ 1 letter
  - Only 12% had change exceeding CoR at Year 4
  - Only 2% exceed FDA threshold of 15 letters

Change from Baseline (ETDRS letters)	Year 2 (N=88)	Year 4 (N=93)
≥ 15	0 (0%)	0 (0%)
10 to 14	1 (1%)	0 (0%)
5 to 9	3 (3%)	2 (2%)
-4 to +4	65 (74%)	55 (59%)
-9 to -5	15 (17%)	28 (30%)
-14 to -10	4 (5%)	6 (6%)
≤ -15	0 (0%)	2 (2%)

CoR: 8.8 letters

Ellipsoid zone area

- Floor effect (<3mm^2) impacted 67% of cohort
- Among those with EZ>3mm^2, standardized rate of change was lower (less change/more variability) than all other measures except BCVA

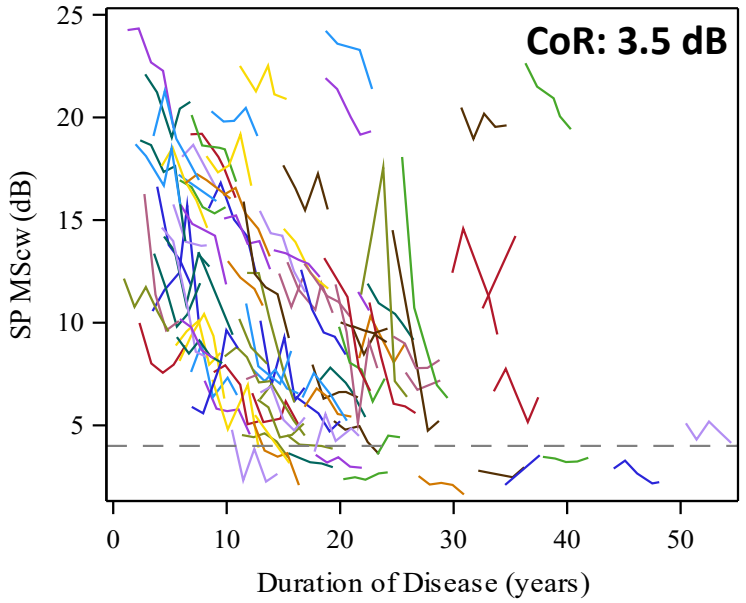


CoR: Coefficient of repeatability; EZ: Ellipsoid zone

Visual field mean sensitivity (MS) has favorable endpoint properties in *USH2A*-related IRD

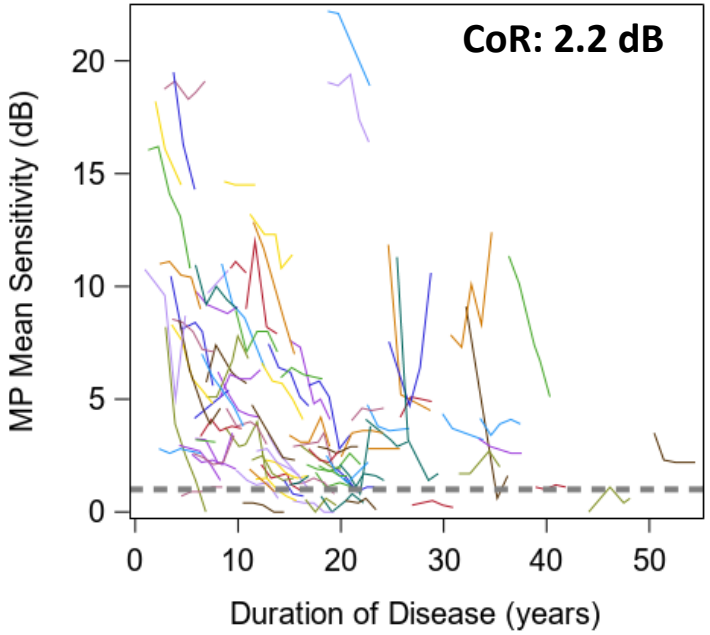
Static Perimetry MS_{CW}

- Correlated with duration of disease (r=-0.41)
- Minimal floor effect (10%)
- 19% of eyes had change > CoR at Year 4
- **Highest standardized rate of change**
- The volumetric measures had no advantages over MS for assessing change over time



Microperimetry MS

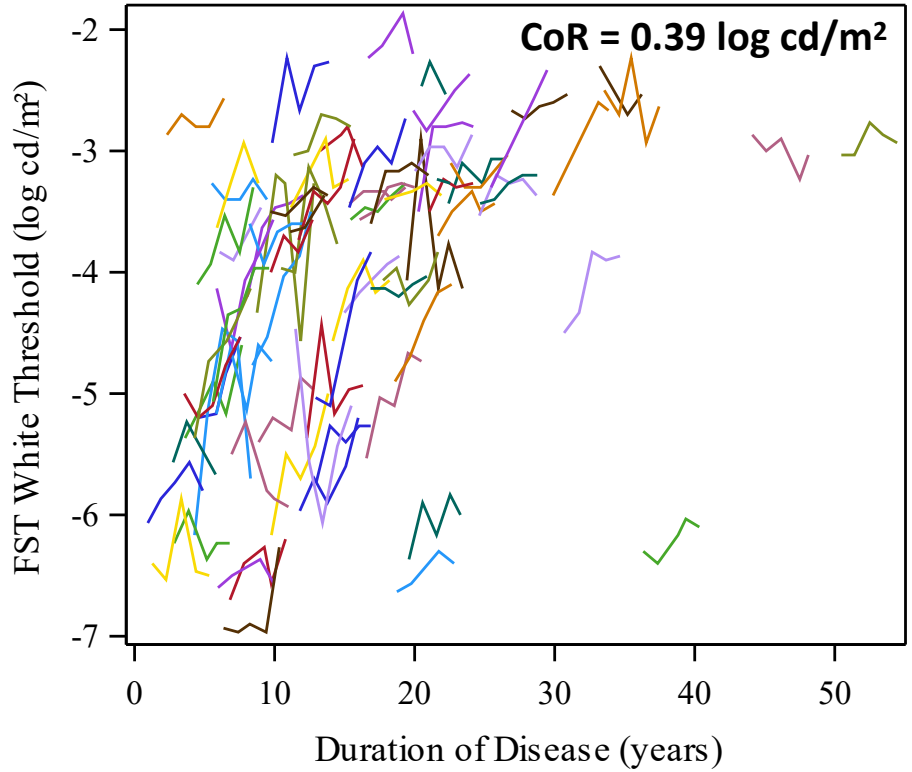
- Correlated with disease duration (r=-0.33) and baseline EZ area (r=0.67)
- Minimal floor effect (9%)
- **32% of eyes had change > CoR at Year 4**
- High standardized rate of change



CoR: Coefficient of repeatability
MS: Mean sensitivity

Full-field stimulus threshold (FST) has desirable endpoint qualities in *USH2A*-related IRD

- Correlated with baseline EZ area (r=-0.73) and disease duration (r=0.51)
- Negligible floor effect
- High standardized rate of change
- Low test-retest variability
- Highest percentages of eyes exceeding CoR at Year 2 (30%) and Year 4 (47%)



CoR - Coefficient of repeatability

REDI Initiative #1: RUSH2A Endpoints
Key Takeaways


tvst
Retina

Endpoints and Design for Clinical Trials in *USH2A*-Related Retinal Degeneration: Results and Recommendations From the RUSH2A Natural History Study

Maureen G. Maguire[1], David G. Birch[2], Jacque L. Duncan[3], Allison R. Ayala[1], Lauren N. Ayton[4], Janet K. Cheetham[5], Peiyao Cheng[1], Todd A. Durham[5], Frederick L. Ferris, III[6], Carel B. Hoyng[7], Rachel M. Huckfeldt[8], Glenn J. Jaffe[9], Christine Kay[10], Eleonora M. Lad[9], Bart P. Leroy[11], Wendi Liang[1], Lee S. McDaniel[1], Michele Melia[1], Michel Michaelides[12], Mark E. Pennesi[2,13], José-Alain Sahel[14–16], and Lassana Samarakoon[1], on behalf of the REDI Working Group and the Foundation Fighting Blindness Clinical Consortium Investigator Group

Maguire MG et al Transl Vis Sci Technol 2024; 13(10): 15; **PMID:** 39382872

In *USH2A*-related retinal degeneration:

Visual Acuity

- Changes by 1 letter/year

EZ Area

- Floor effect in 2/3 participants

Microperimetry and Static Perimetry Mean Sensitivity

- Slopes are more sensitive to change than the proportions of eyes exceeding a threshold – ***top choice for USH2A endpoint***!

Full-field stimulus threshold (FST)

- Sensitive even in eyes with early disease

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Microperimetry and Static Perimetry Mean Sensitivity

- Slopes are more sensitive to change than the proportions of eyes exceeding a threshold – ***top choice for USH2A endpoint***!

Full-field stimulus threshold (FST)

- Sensitive even in eyes with early disease

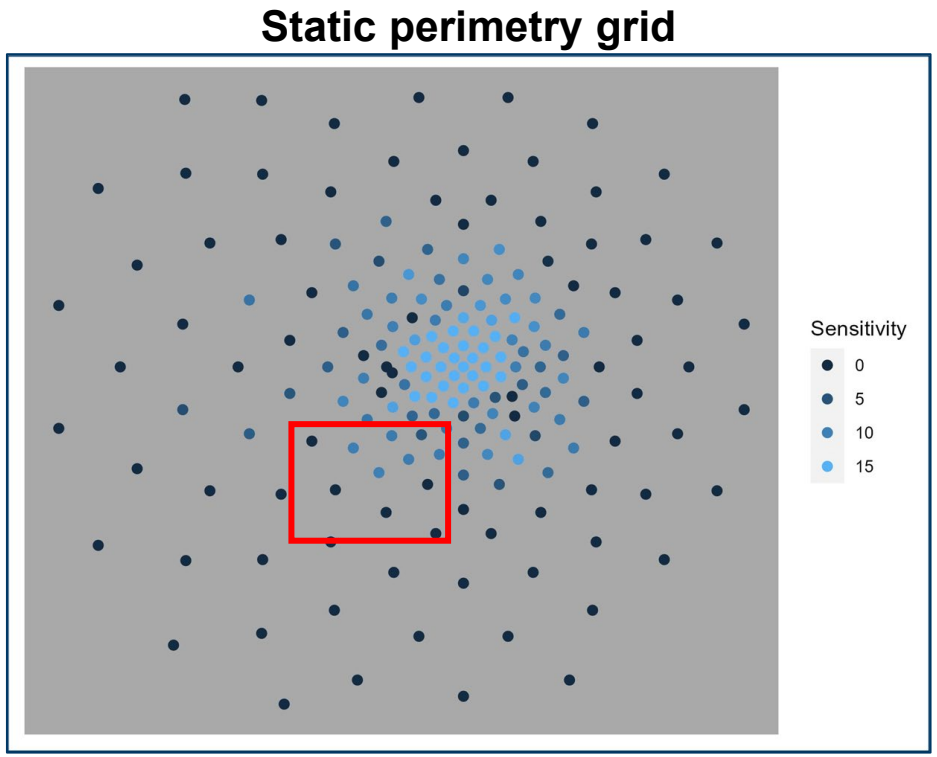
BUT: Changes in mean sensitivity not currently accepted by regulators

Functional Transition Points

- Perimetry endpoint accepted by FDA: Mean change ≥ 7 dB in ≥ 5 pre-specified points
- Not a viable endpoint choice in RUSH2A cohort for progression-slowing intervention

	Static Perimetry		Microperimetry	
Points used →	All points	Central 30°	All points	
2 Years	2%	0%	0%	
4 Years	5%	9%	5%	

- **Can we maximize the chance of meeting the FDA-approved outcome?**
- Basic idea: Identify ≥ 5 points at baseline with the highest chance of losing function over time*



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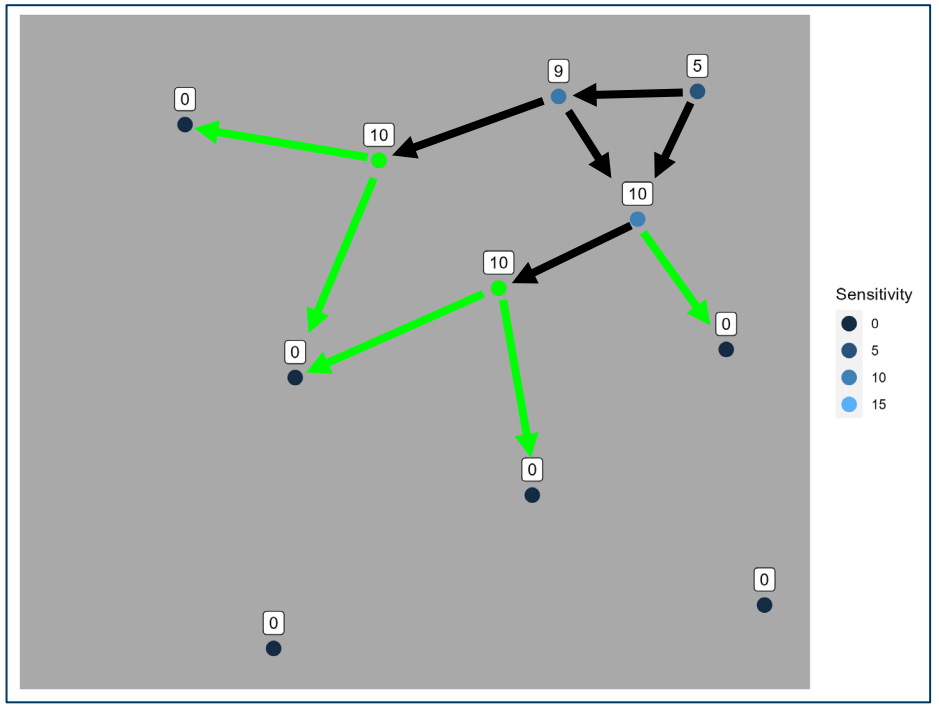
Assessing sensitivity difference



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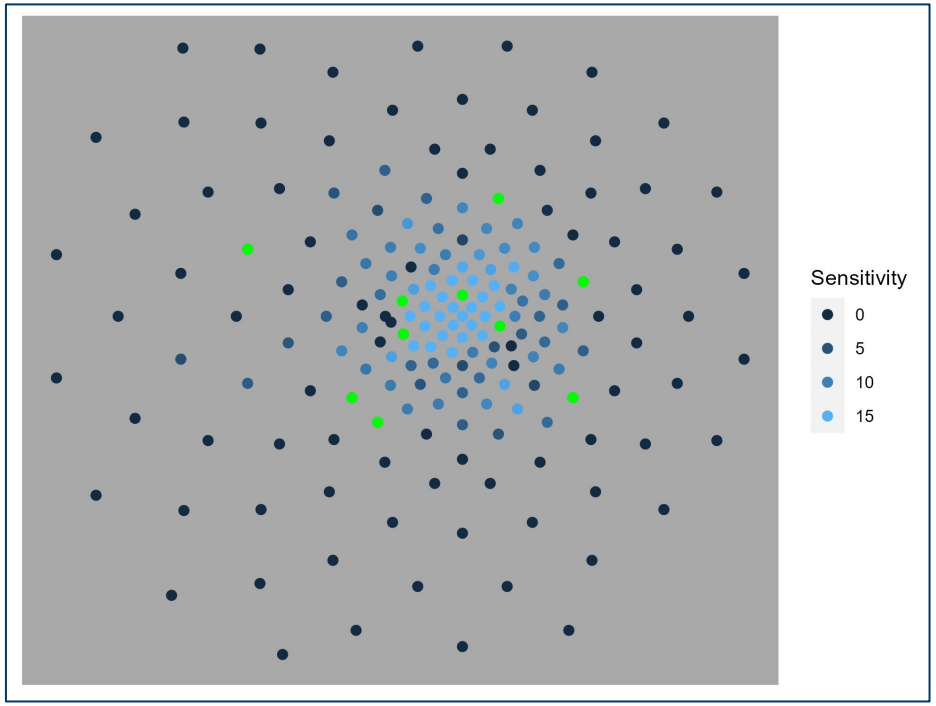
Functional transition points (green)



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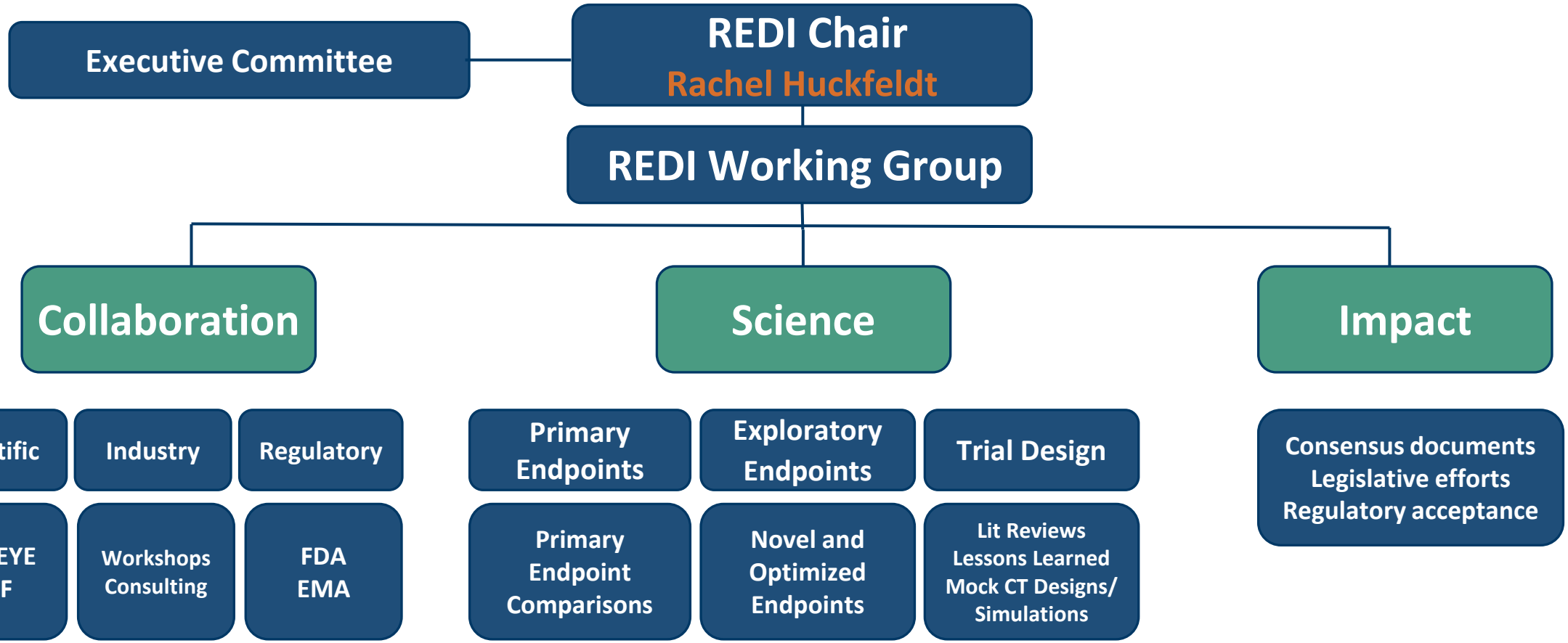
REDI Organization and Initiatives



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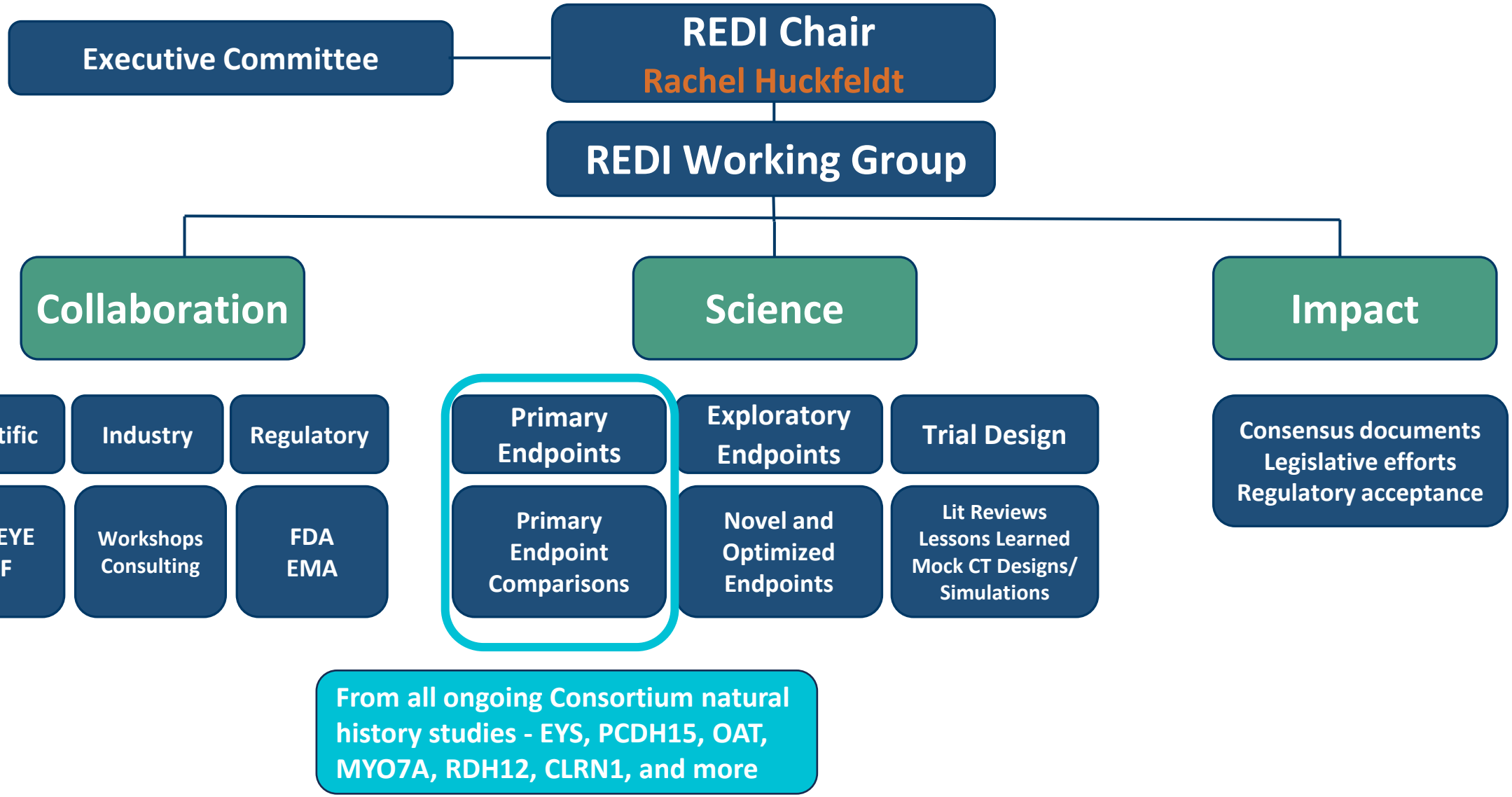

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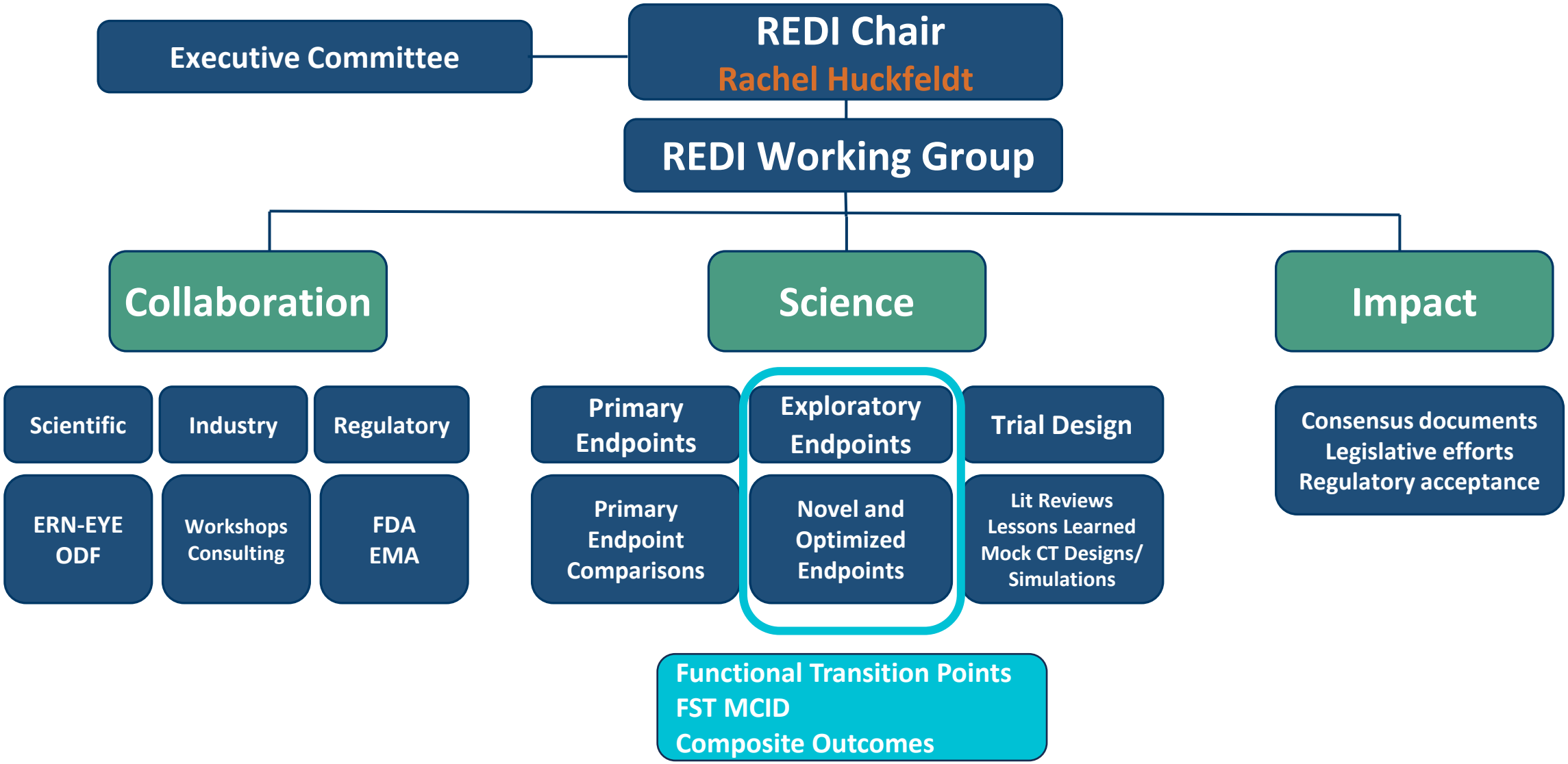

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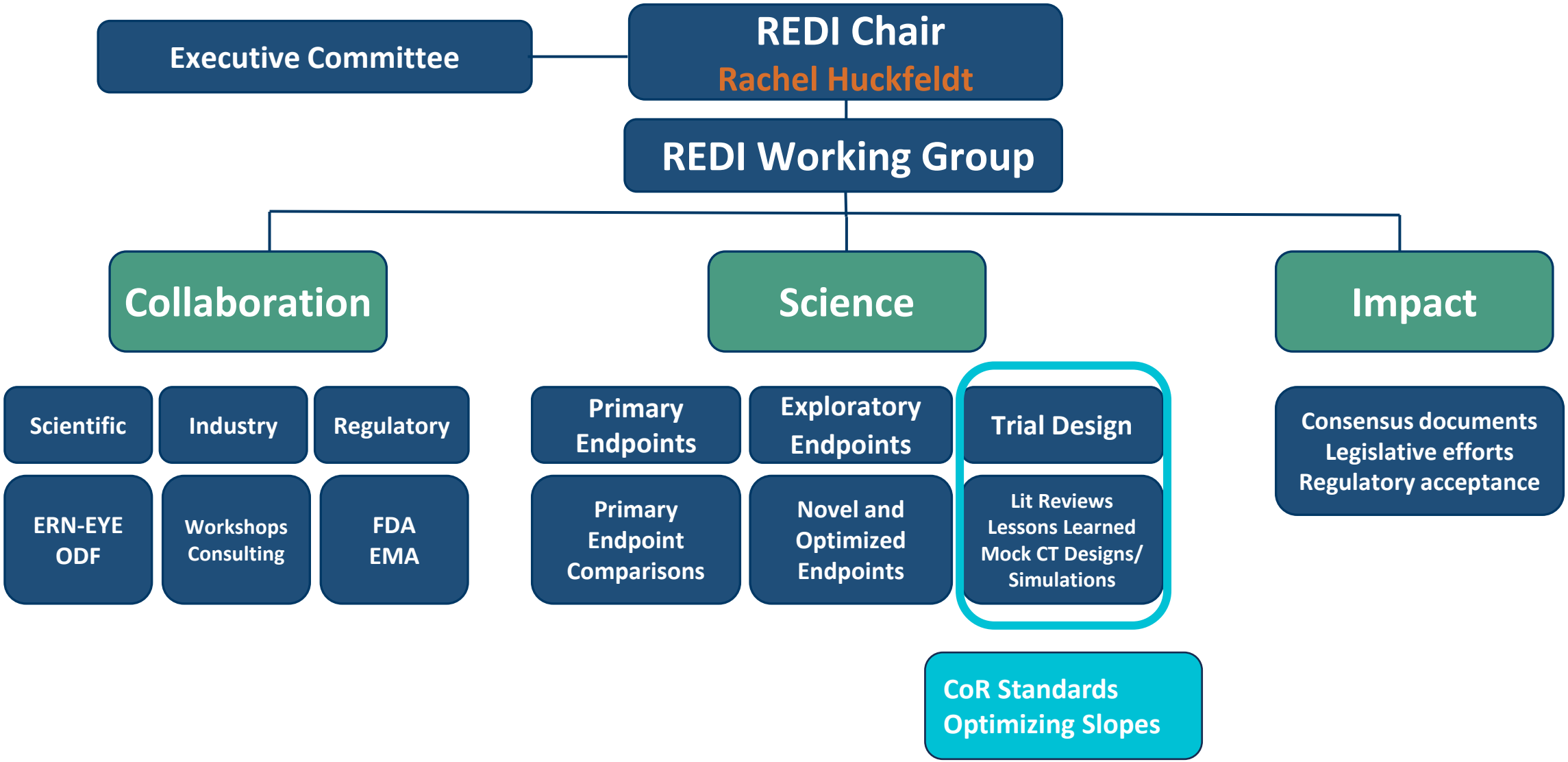

Current REDI Working Group Members

Working Group Members establish objectives, develop analyses and interpretations, pursue regulatory and industry input, and **make final decisions about recommendations**, with oversight from the Consortium Executive Committee (EC).

REDI Chair: Rachel Huckfeldt (EC)
Principal Statistician: Lee McDaniel
Tomas Aleman
Shobana Aravind
Allison Ayala (EC)
Lauren Ayton
Janet Cheetham (EC)
Art Cideciyan
Jacque Duncan (EC)
Todd Durham (EC)
Fredrick Ferris (EC)
Sandeep Grover
Carel Hoyng
Glenn Jaffe
K. Thiran Jayasundera
Christine Kay
Eleonora Lad
Bart Leroy
Yu-Fen Li
Wendi Liang
Michel Michaelides (EC)
Audra Miller
Mark Pennesi (EC)
José-Alain Sahel (EC)
Lassana Samarakoon
Mandeep Singh
Katarina Stingl
Wei Tian

Inaugural REDI Co-Chairs: Maureen Maguire and David Birch