ELEVAIR™ Endobronchial Coil System RENEW Trial Design

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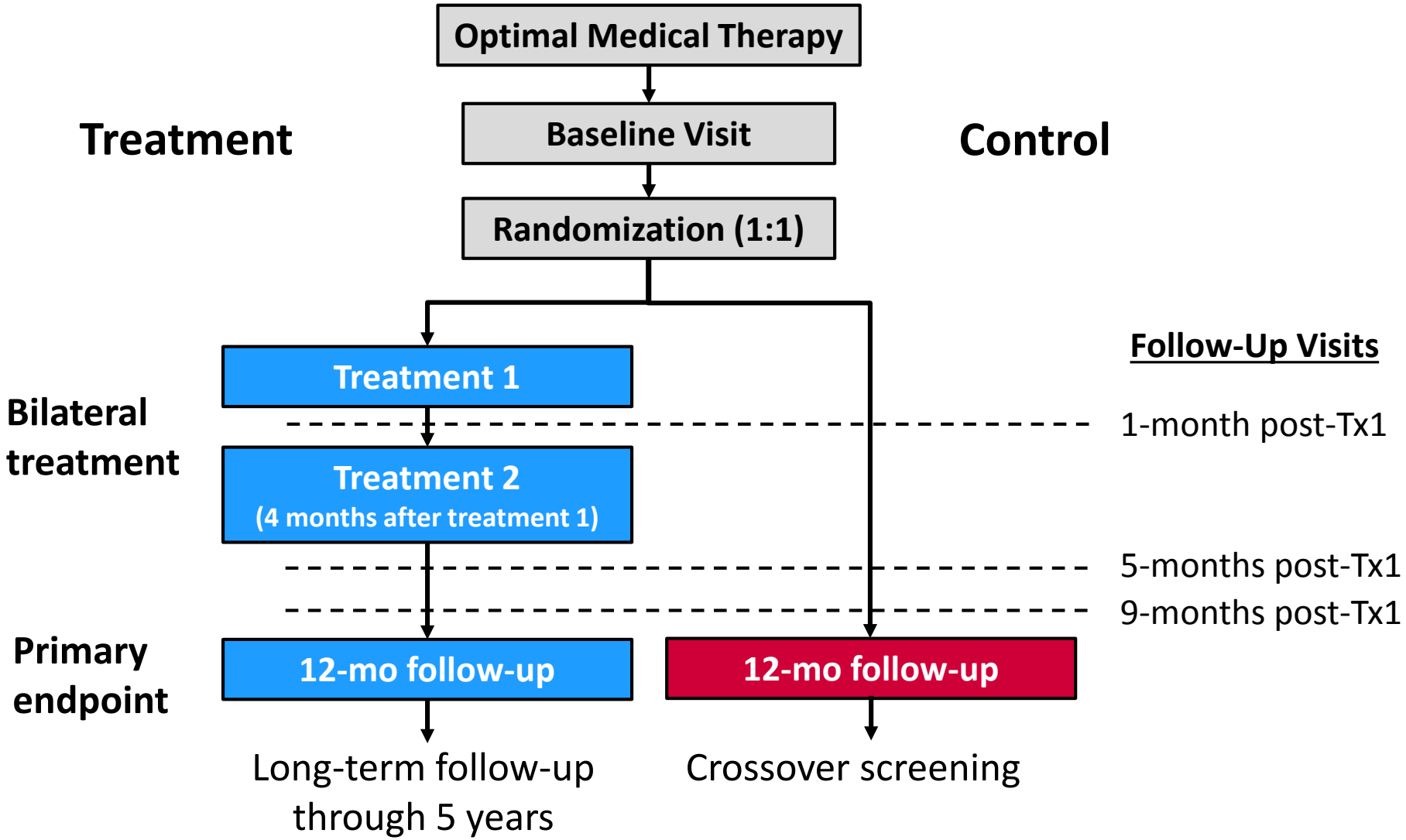
Overview of Trial Design Presentation

- RENEW Trial Design
  - Entry Criteria
  - Effectiveness Endpoints
  - Statistical Methods
  - Pre-specified Subpopulations
- Crossover Study Design

RENEW Pivotal Randomized Trial Design



RENEW Original Key Trial Entry Criteria

Entry criteria

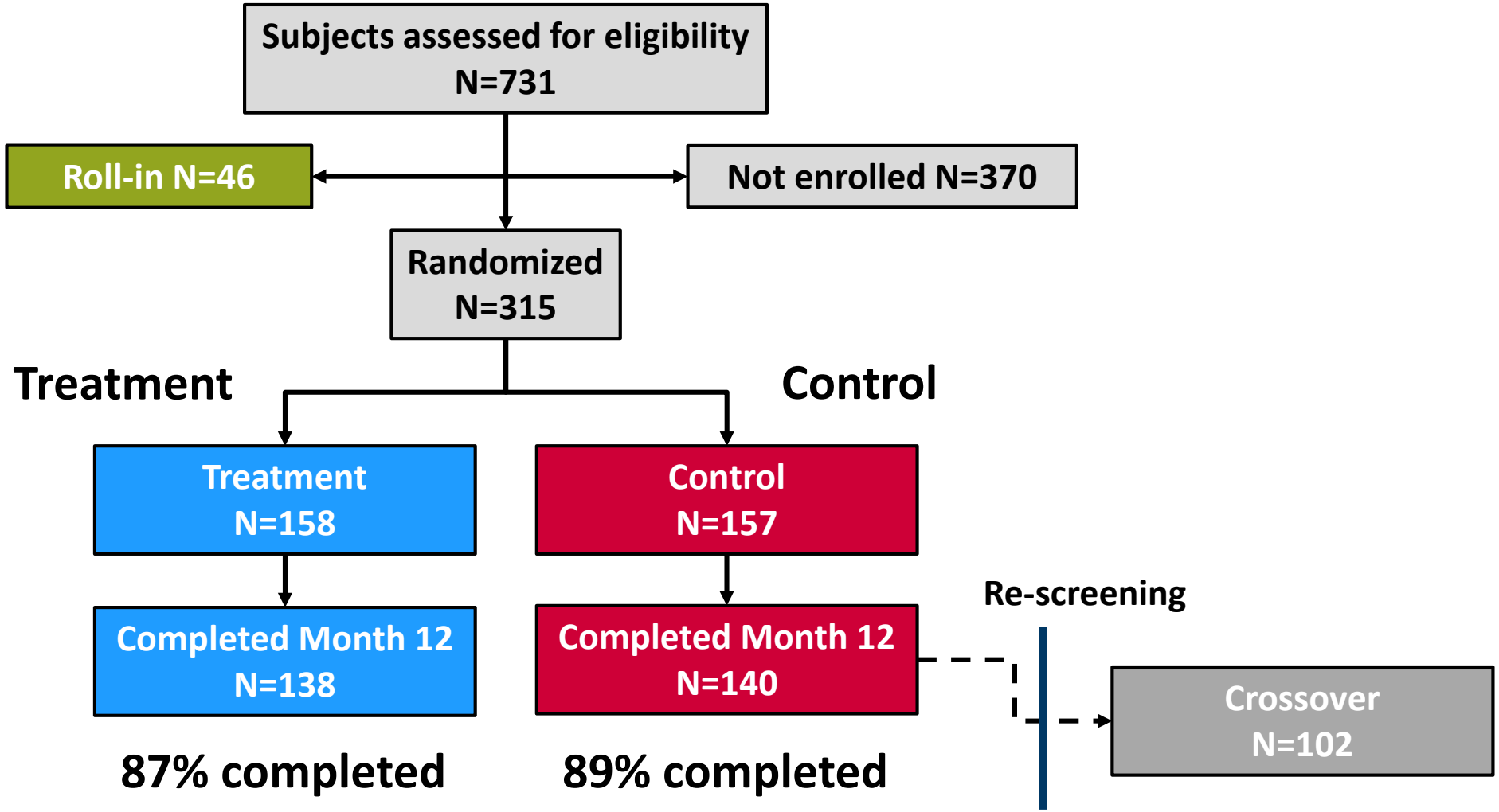
- CT scan indicated bilateral emphysema, as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab"
- FEV_1 ≤45% predicted
- Dyspnea scoring ≥2, mMRC scale 0-4
- Smoking cessation ≥8 weeks prior
- Pulmonary or maintenance respiratory rehabilitation
- Ability to walk >140 meters (150 yards) in 6 minutes
- RV ≥225% predicted

RENEW *Amended* Key Trial Entry Criteria

Entry criteria

- CT scan indicated bilateral emphysema, as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab"
- FEV_1 ≤45% predicted
- Dyspnea scoring ≥2, mMRC scale 0-4
- Smoking cessation ≥8 weeks prior
- Pulmonary or maintenance respiratory rehabilitation
- Ability to walk >140 meters (150 yards) in 6 minutes
- ~~**RV ≥225% predicted**~~ **RV ≥175% predicted**

RENEW Consort Diagram



RENEW Effectiveness Endpoints

Primary Endpoint

Δ6MWT at 12 months

Secondary Endpoints

%ΔFEV_1

ΔSGRQ

% 6MWT responders (≥25 m)

Additional Exploratory Effectiveness Endpoints

ΔRV

ΔRV/TLC

% SGRQ responders (≤ -4 points)

RENEW Effectiveness Endpoints
Family-wise Type 1 Error Control

Primary Endpoint

ΔSixMWT at 12 months

If significant at α=0.025 1-sided

Secondary Endpoints

$\%\Delta FEV_1$

ΔSGRQ

% 6MWT responders (≥25 m)

Hochberg step-up procedure at α=0.025 1-sided

Additional Exploratory Effectiveness Endpoints

ΔRV

ΔRV/TLC

% SGRQ responders (≤–4 points)

No alpha-control

RENEW Effectiveness Analysis Methods

Non-parametric Rank ANCOVA

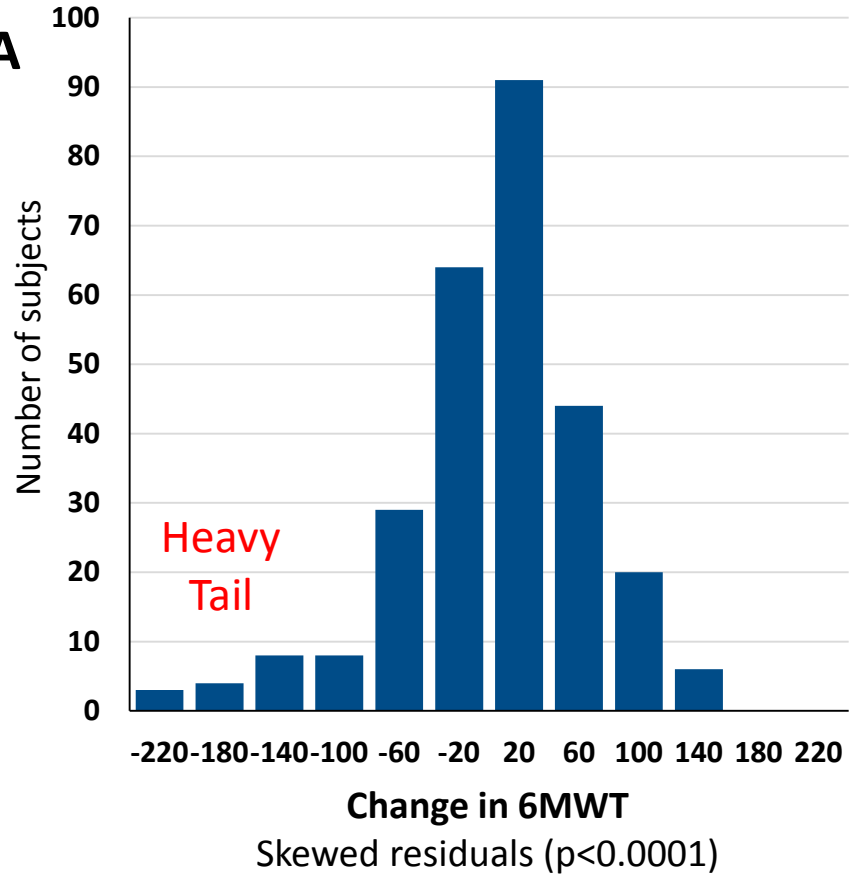
- Δ6MWT
- % ΔFEV_1

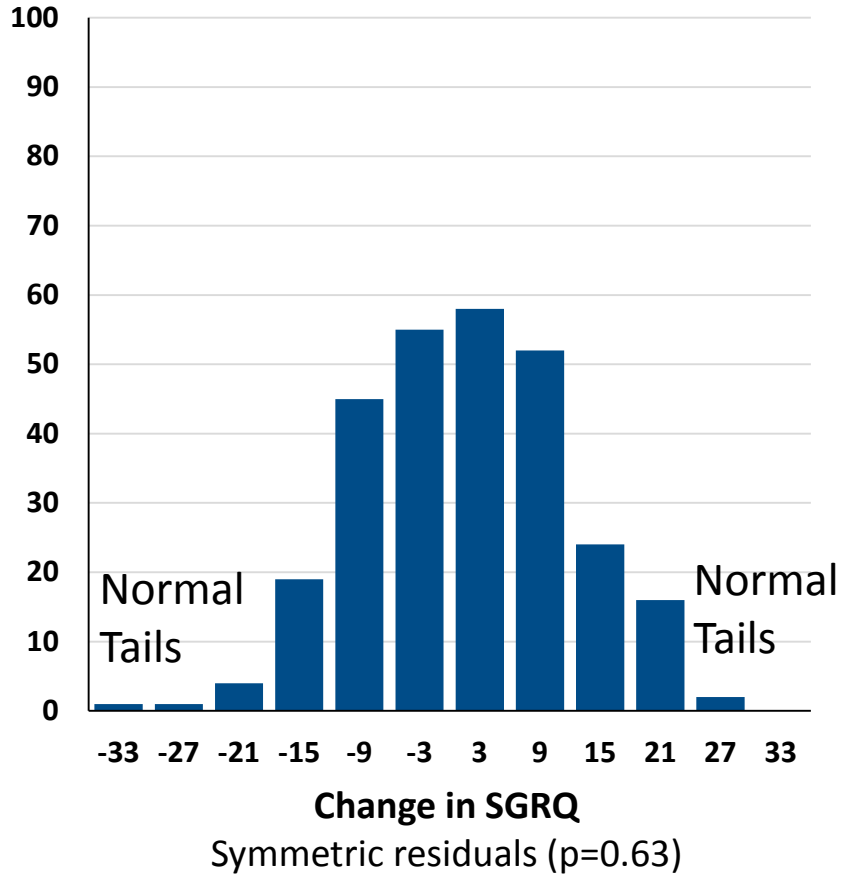
Parametric ANCOVA

- ΔSGRQ

Logistic Regression

- % 6MWT responders





Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

RENEW Effectiveness Analysis Methods

Primary Endpoint

- Δ6MWT at 12 months

Secondary Endpoints

- %ΔFEV$_1$
- ΔSGRQ
- **% 6MWT responders (≥25 m)**

Additional Exploratory Effectiveness Endpoints

- ΔRV
- ΔRV/TLC
- **% SGRQ responders (≤ -4 points)**

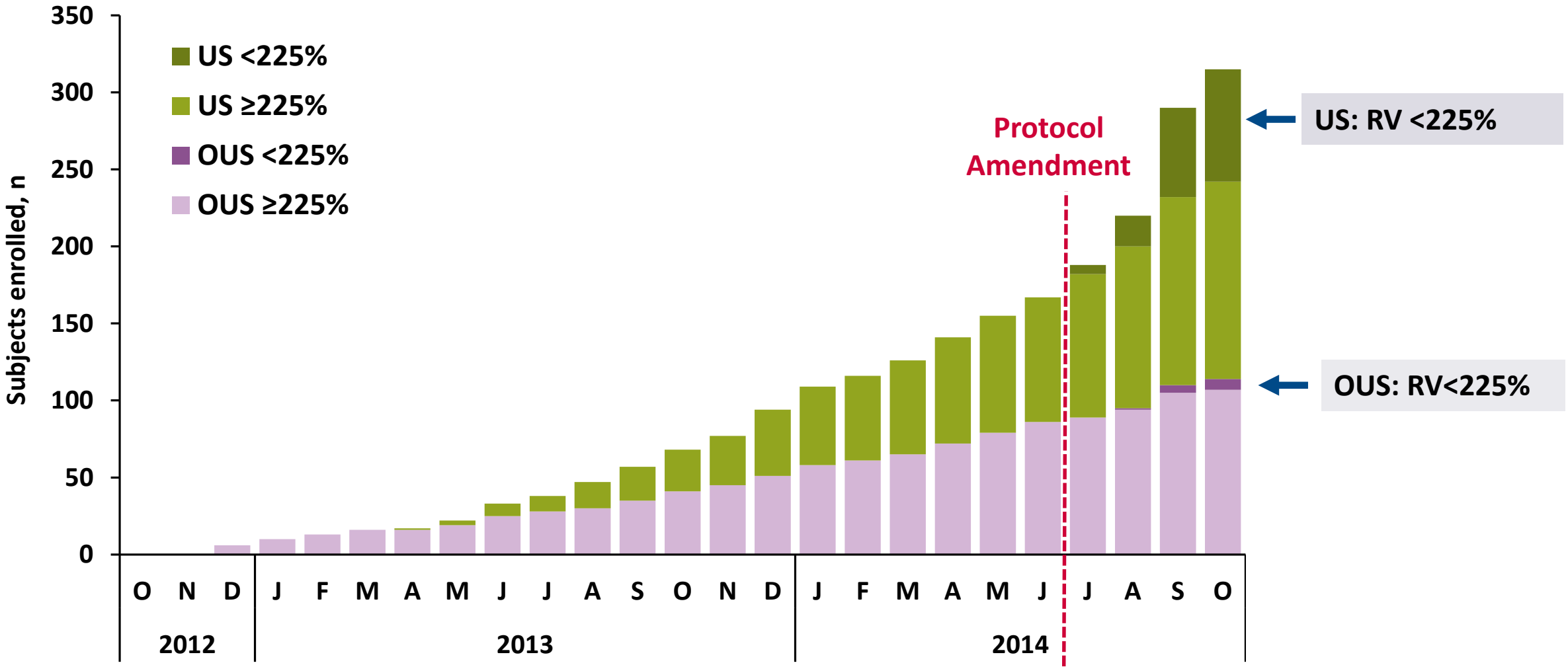
Responder rate analysis

- Clinically meaningful benefit to the subject
- Direct measure of clinical significance

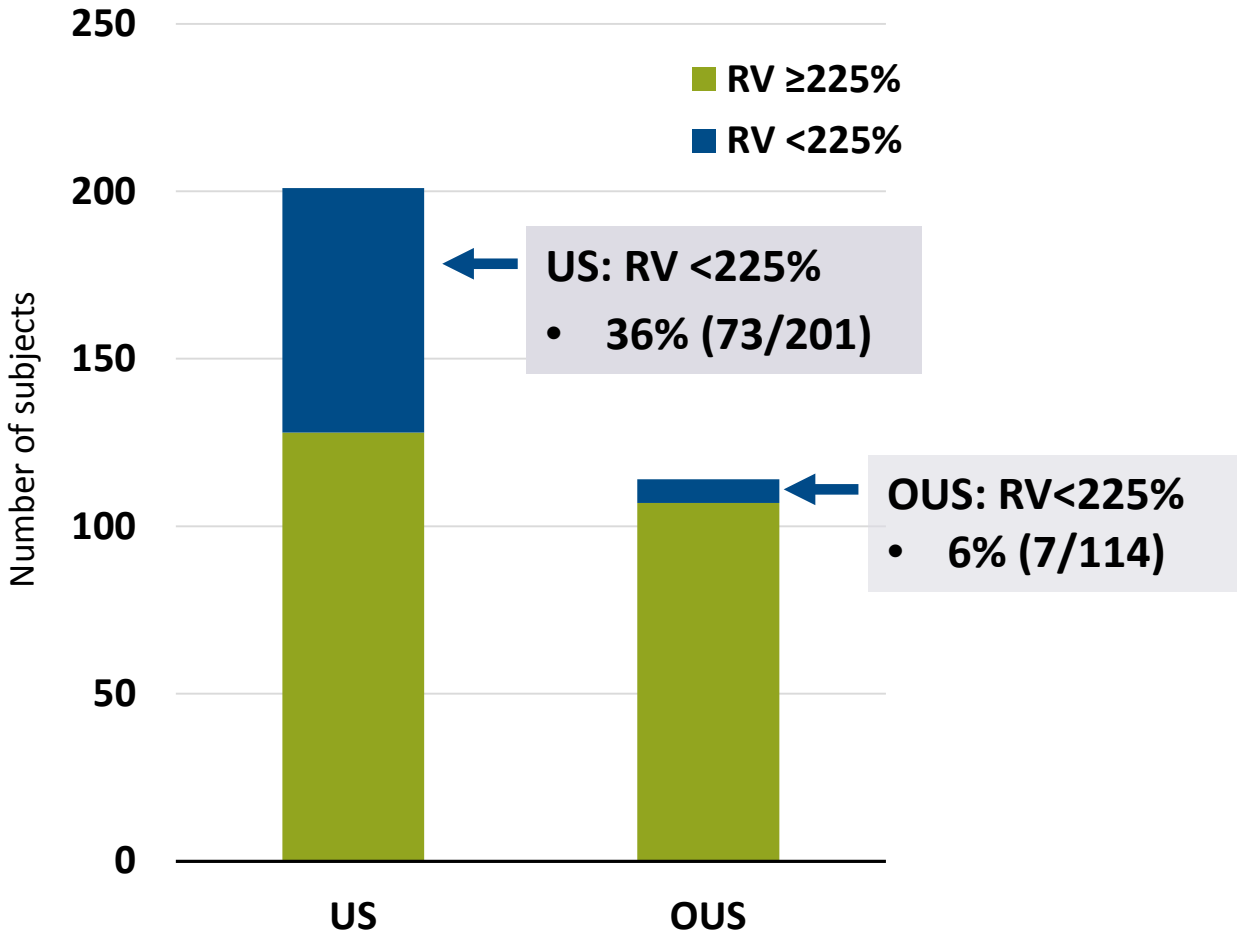
Pre-specified Subpopulations Not Alpha-Controlled

- Baseline RV status: RV ≥225% vs RV <225%
- Region: US vs OUS
- Disease status: homogeneous vs heterogeneous
- Gender: male vs female

Enrollment in RENEW by Region (OUS vs US) and RV (<225% or ≥225%)



Imbalance of RV (<225% or ≥225%) by Region (OUS vs US)



- Regions were highly imbalanced by baseline RV status
- US enrolled substantially more subjects with RV <225%
- This imbalance drives regional differences in effectiveness

See slides CD-28 through CD-30.

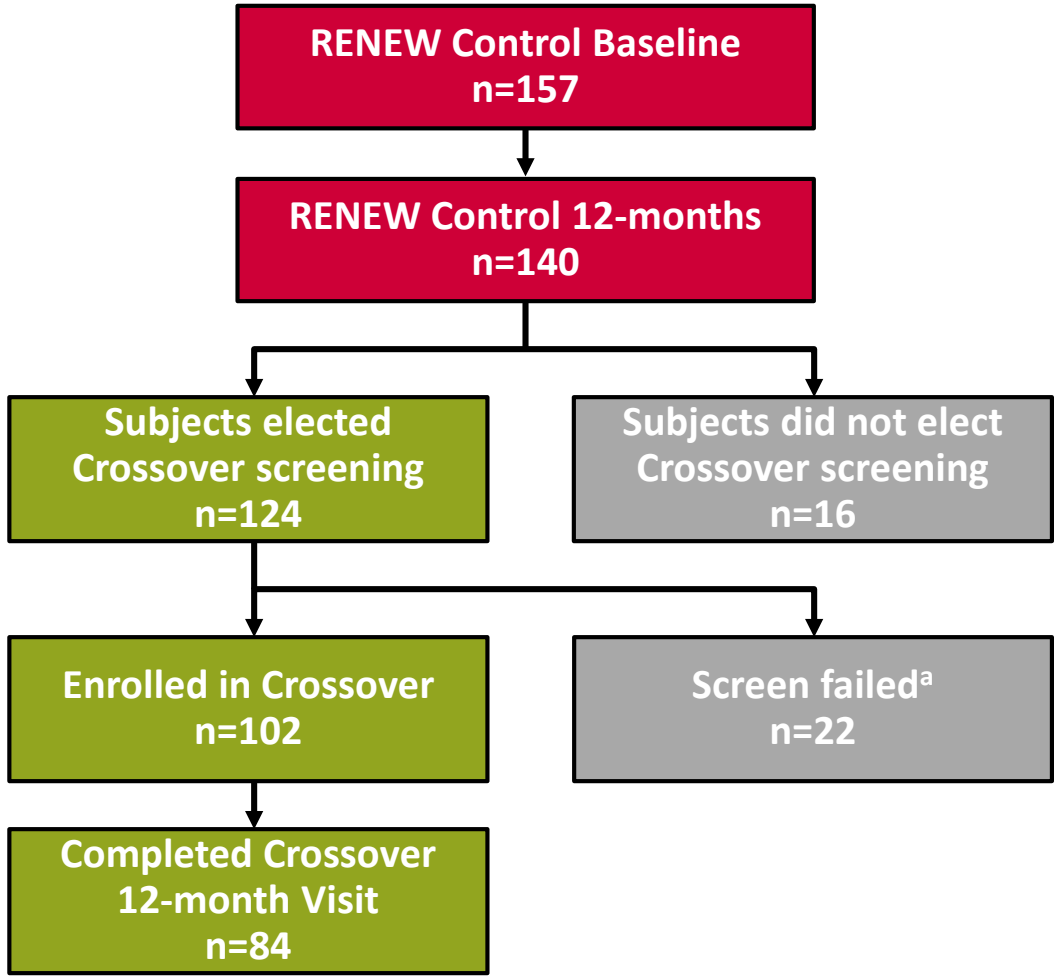
Note: Figure was not provided within the PMA; however, underlying information / analysis was included.

Scientific Credibility of the RV ≥225% Subpopulation

- The trial met the primary analysis for the entire ITT population
- Reduction in RV is the mechanism of action of the coils
- RV ≥225% was the original population and 75% of total enrollment
- Empirical evidence supports the increasing differential benefit for the coils for RV

Crossover Study

- RENEW control group that met similar entry criteria
- Single-armed, observational cohort, with no concurrent control
  - Scientific limitations compared to randomized controlled trials
- Of the 157 controls, 102 subjects crossed over
  - Self-selected, positive performers
  - Potential mathematical regression-to-the-mean
  - Disease progression over time



[a]1 subject passed screening, but was not enrolled due to physician decision.