Models of Industry Trials for Regulatory Purposes (Safety)

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Safety Evaluation is Not Completed at Approval

- Phase 3 programs evaluate efficacy and general safety/tolerability under constrained circumstances
  - trials enroll hundreds to several thousand
  - fairly limited duration of therapy
  - Inclusion/exclusion criteria narrow to evaluate a homogenous population (e.g., comorbidity exclusion)
  - Specific clinic visits and testing do not mirror real world use

- Post-Marketing Requirements typically deal with specific or narrow topics for clinical trials
  - Drug-drug interactions
  - Special populations (e.g., renal impaired, etc.)
  - Pediatric populations

Observational Studies Have Been Increasingly Used to Continue Safety Evaluation

- Evaluate associations with rare events or long-latency outcomes
- Evaluate real-world populations and actual drug use conditions

But…

- Can easily fall prey to unmeasured confounding influences
- Easy to miss, even relatively large, signals
- Identify a potential signal that is not substantiated by randomized data

Large Simple Trial (LST) Principles Are Rarely Used to Continue Safety Evaluation in Post-Approval Setting

- Minimize bias associated with observational data by using prospective design , control, and randomization

- Design intended to be highly relevant to real world clinical practice
  - Large sample size
  - Broad entry criteria consistent with labeling
  - Minimal data collection requirements during routine clinical care
  - Typically requires ‘hard endpoints’ that are simple to ascertain

- Only a handful of LSTs directed at ‘Safety’ questions over last 20 years
  - E.g., COSMIC, ZODIAC, HYPREN, PAIN, SMART

In Some Therapeutic Areas, Large-Scale RCTs are Required to Evaluate Safety Pre-Approval

- Phase 3 programs in dyslipidemia now routinely include CV outcomes trials enrolling up to 20,000 subjects

- Since 2008, drug approvals in Type 2 Diabetes requires pre-approval CV data to rule out an 80% increase in CV risk compared to placebo
  - Typically requires between 5,000-10,000 subjects
  - Final, post-approval data required to rule out a 30% increase in risk

- High cost (~$300M++) and duration of these drug development programs limit such investigations only to therapeutic areas with enough commercial potential to provide reasonable return on investment

LST Can Yield Opportunity in both Pre/Post-Approval Safety Evaluation

- Where question at hand is limited in nature (e.g., cardiovascular risk)
- Where underlying occurrence is relatively uncommon
- Where there is an interest in safety under real world conditions

Orexigen's Contrave: Example of Modified LST to Address Outstanding Safety Questions

- Orexigen filed NDA in 2010 for an obesity therapeutic, naltrexone/bupropion (Contrave ®)

- FDA expressed concern for theoretical CV risk based on known impact of bupropion on BP (~1-2 mmHg) and HR (~1.5 bpm)

- Agreement reached for pre-approval CV safety information, similar to current guidance in T2DM
  - Approval can be based upon interim analysis data ruling out a doubling of CV risk compared to placebo (i.e., upper bound of 95% CI must be <2.0)

Contrave CV Trial Design Incorporated Extensive Discussion with FDA

- Agreement on singular focus of safety
- Determination of risk thresholds to exclude at both interim analysis (exclude HR ≥2.0) and final analysis (exclude HR ≥1.4)
- General protocol details addressed through written correspondence with FDA's Office of new Drugs
  - Specific discussion on ITT vs. Per-Protocol analysis and real world utilization with the early evaluation approach
- Special Protocol Assessment agreement with Review Division (Division of Metabolism and Endocrinology Products)
  - ITT is primary analysis to support approval
  - Per-Protocol is a secondary analysis

Orexigen Applied LST Principles to Pre-Approval CV Safety Requirement

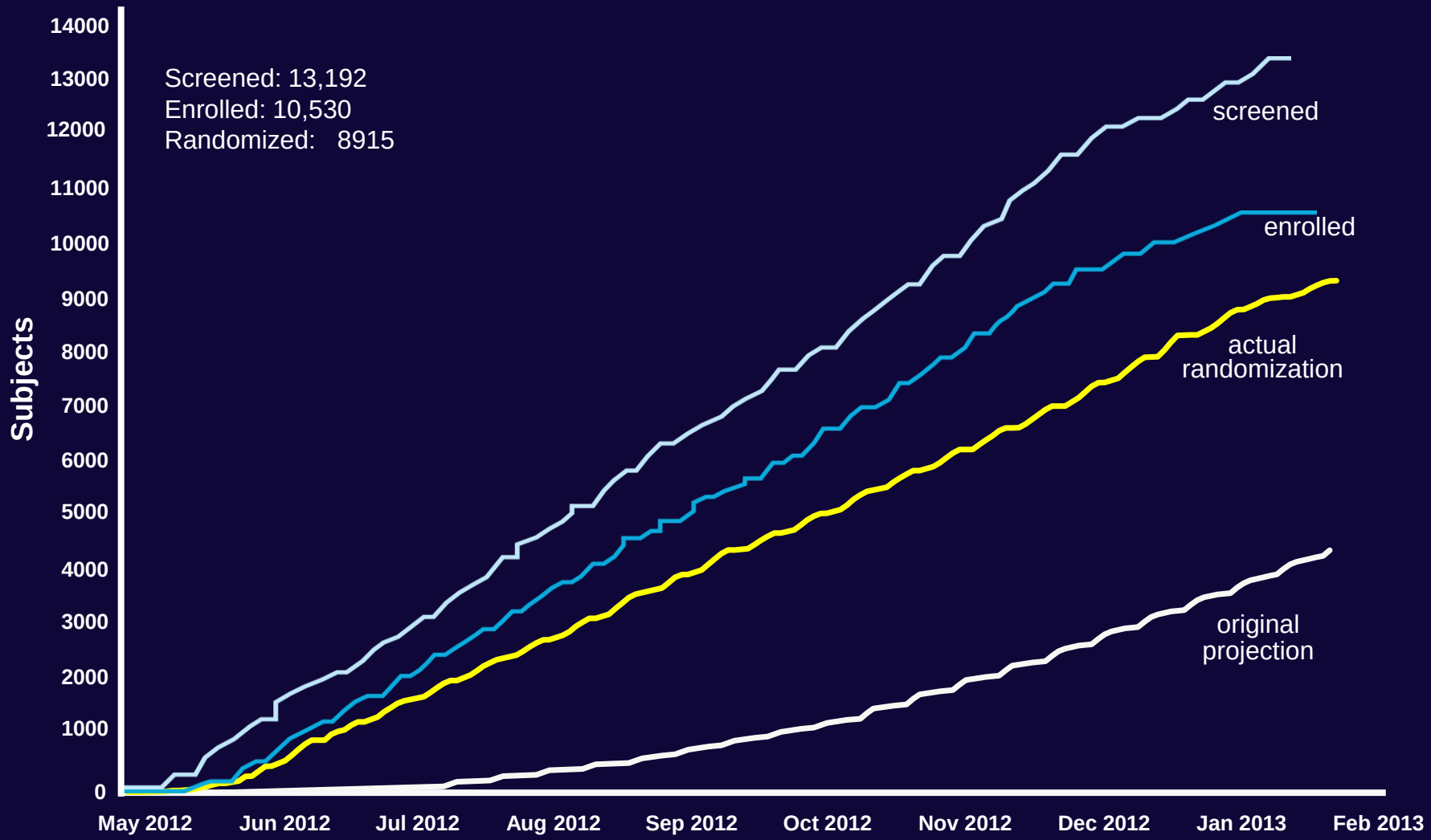
- Simplified I/E criteria compared to Phase 3
  - Still required higher background CV risk
- Streamlined data collection
  - No labs, ECGs after baseline
  - Collect only SAE and potential MACE
  - Infrequent study visits (q6 m), supplemented by electronic query regarding hospitalization
- Risk-based clinical site monitoring
- Standard RCT elements:
  - Double-blind, placebo controlled
  - Scheduled study visits vs. routine clinical care

Real World Utilization Tested Using a Post-Randomized Evaluation

- In the real world, patients are unlikely to continue an obesity therapy in absence of any weight loss
  - Key criticism of SCOUT, a trial demonstrating small CV risk with an obesity drug (sibutramine)
    - >70% of subjects did not have clinically meaningful weight loss but stayed on therapy
    - Post-hoc analysis demonstrated risk concentrated in these non-responders

- Contrave CV trial incorporates early evaluation for weight loss and blood pressure
  - week 16 evaluation for exclusion
  - both Contrave and placebo arms
  - at least 2% bodyweight
  - no sustained increases in blood pressure (≥10 mmHg, either diastolic or systolic)

Rapid Enrollment in a US-Only Trial Using Modified LST Approach



Summary: LST Approaches for Safety Evaluation

- True LSTs are infrequently used for primary safety evaluations
- Increasing requirement for ruling out low frequency safety signals in certain therapeutic areas should stimulate interest in using modified LST approaches
- Recognition that aspects of real world utilization can (and should) be incorporated into safety study designs may result in more generalizable results