



3RD ANNUAL

Nano-rare Patient Colloquium 2025

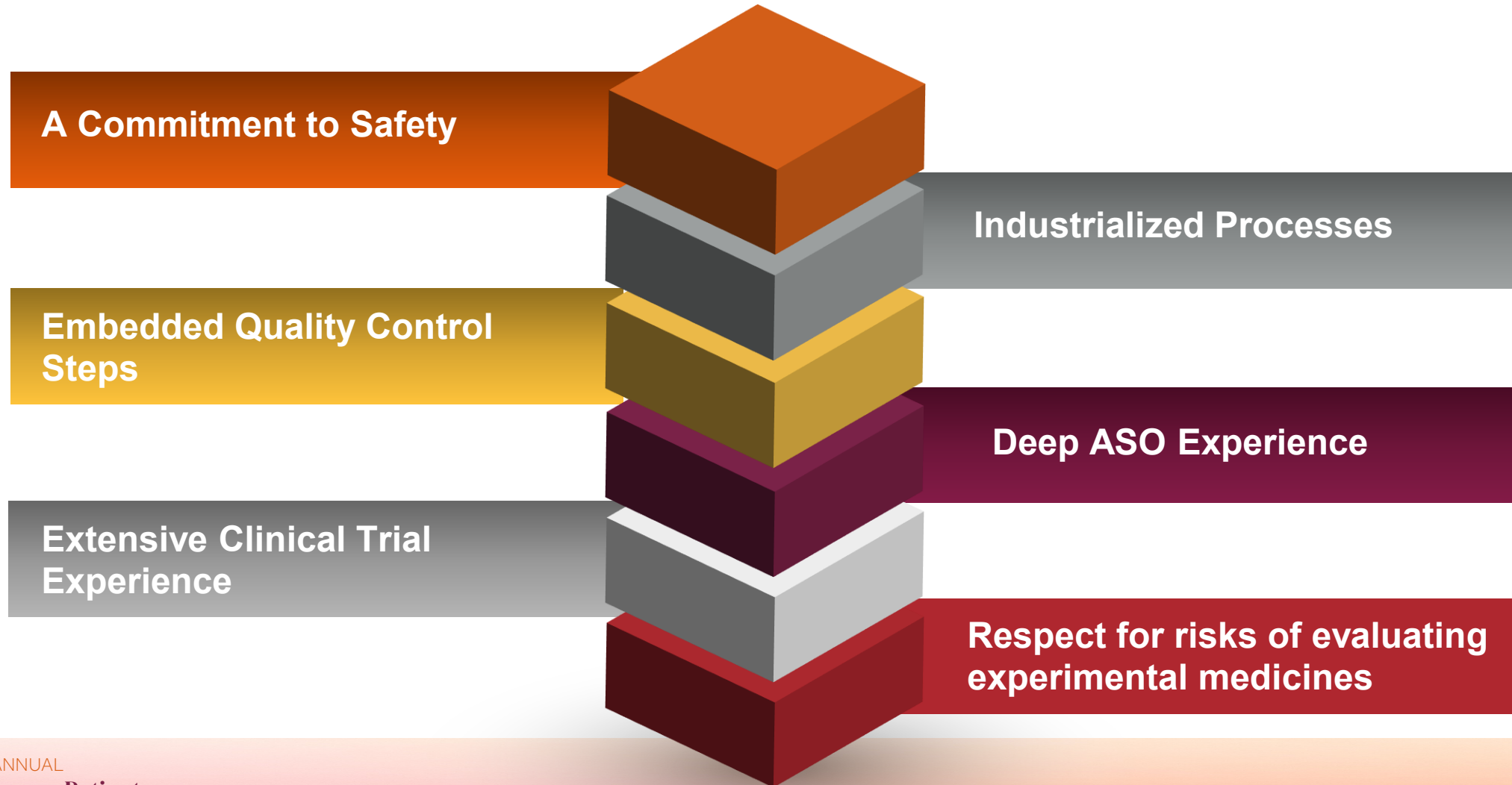
Every Step Matters: How Safety Shapes Our ASO Program Decisions from Discovery to Delivery

Sarah Glass, PhD
Chief Operating Officer, n-Lorem

Safety for our Patients is n-Lorem's Highest Priority

- Begins with a **commitment to avoiding unnecessary side effects** and building industrialized systems with embedded quality-control steps
- **Spans** patient review for acceptance *through* long-term treatment
- Requires a **deep understanding** of each patient's genotype, phenotype and antisense technology
- Overall safety is dependent upon the **quality** of each step and a deep understanding of the **patient's treatment goals**
- Risk / benefit judgements must be made in the context of the **needs of each patient** according to their specific phenotype

High-Quality Judgements are Dependent Upon a Constellation of Factors



Benefit vs. Risk – The Core Lens

- Every decision made for a patient program at n-Lorem is driven by **benefit : risk**.
- This ratio drives both research choices and patient decisions.



By the end of this session, you will:

- I. Understand **what decisions are made at each step** in the n-Lorem process and how they are driven by patient safety
- II. Have a clear picture of **the thought process and expertise** needed at each step
- III. Gain insight into n-Lorem portfolio-wide **metrics and specific examples** of challenging decisions that were made to protect patient safety
- IV. Increase awareness of what n-Lorem has **learned** and how we **improve our efforts** for each subsequent patient based on those learnings

Key Decision Points Throughout the n-Lorem Process are Underpinned by Safety

Anchored by External Review Checkpoints

Real-time evaluation of benefit : risk on treatment


Clinical Protocol Implementation


Patient Review and Acceptance Decision

Whether the risk/benefit is appropriate for the patient to be accepted into the n-Lorem portfolio

FDA Review and Authorization of the IND


Regulatory Strategy and Authorization


Optimal ASO Identification

Identify the optimal ASO for this patient

DECISIONS underpinned by SAFETY



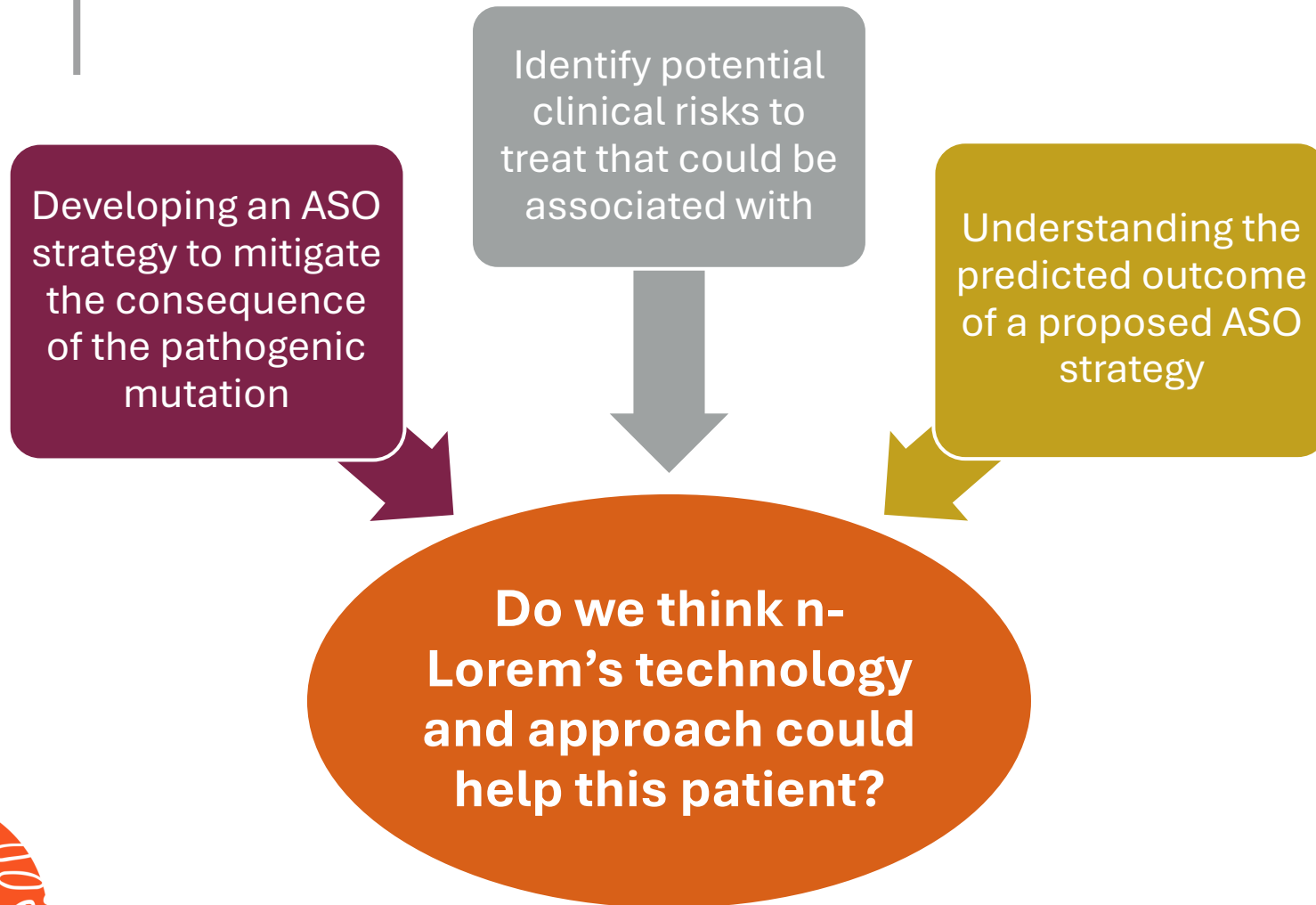
3RD ANNUAL

Nano-rare Patient Colloquium 2025



Patient Acceptance and Target Selection

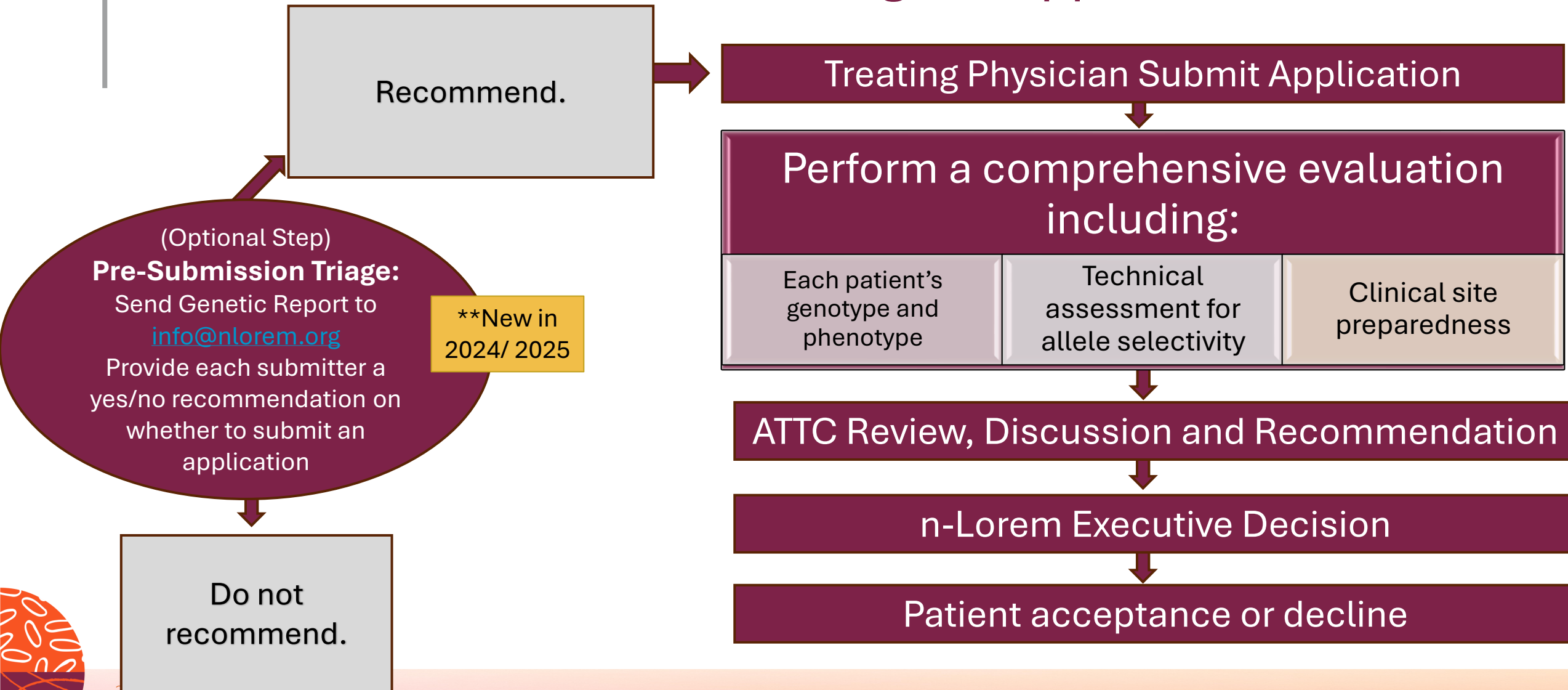
Safety is Prioritized During Patient Evaluation and Review for Acceptance Decision



Expertise Required

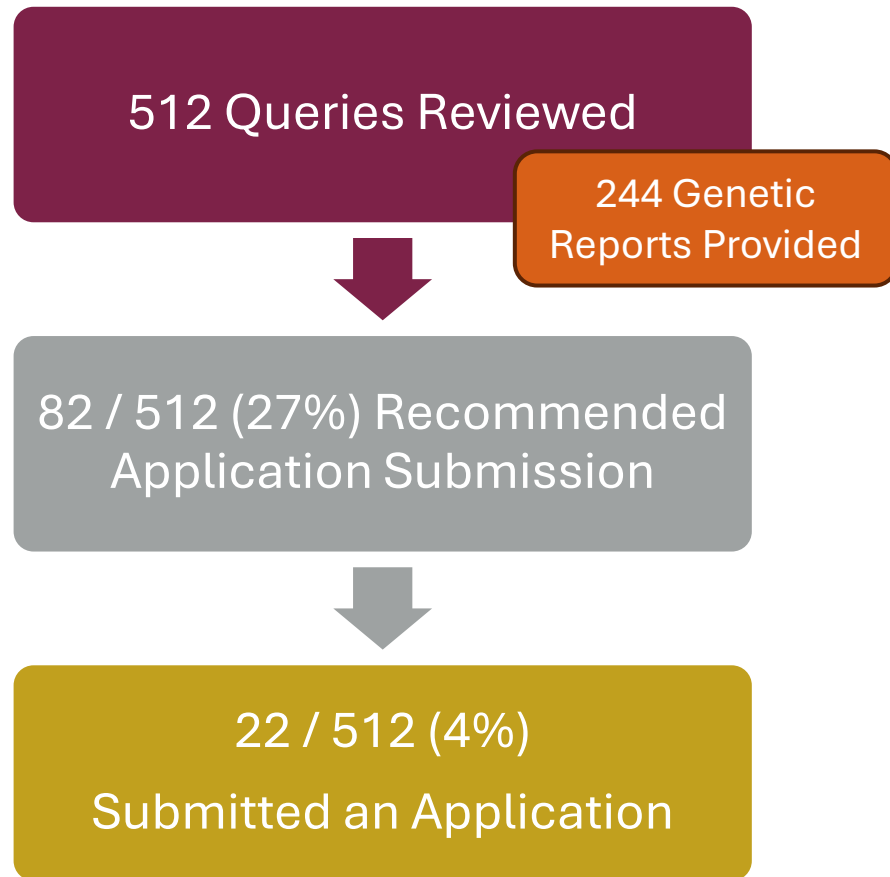
- ASO feasibility
- Clinical/medical genetics
- Neurologists, ophthalmologist, nephrologist, other TAs
- Bioethics
- Antisense technology
- Clinical development and operations

Each Stage in the Process has Defined and Distinct Outcomes: Pre-submission Triage to Application



A Bias to say 'Yes': Pre-Submission Review

Example: Thorough Evaluation of Every POLR3B Patient to Find the Rare Few with ASO-Amenable Mutations



Example: Mutations in POLR3B

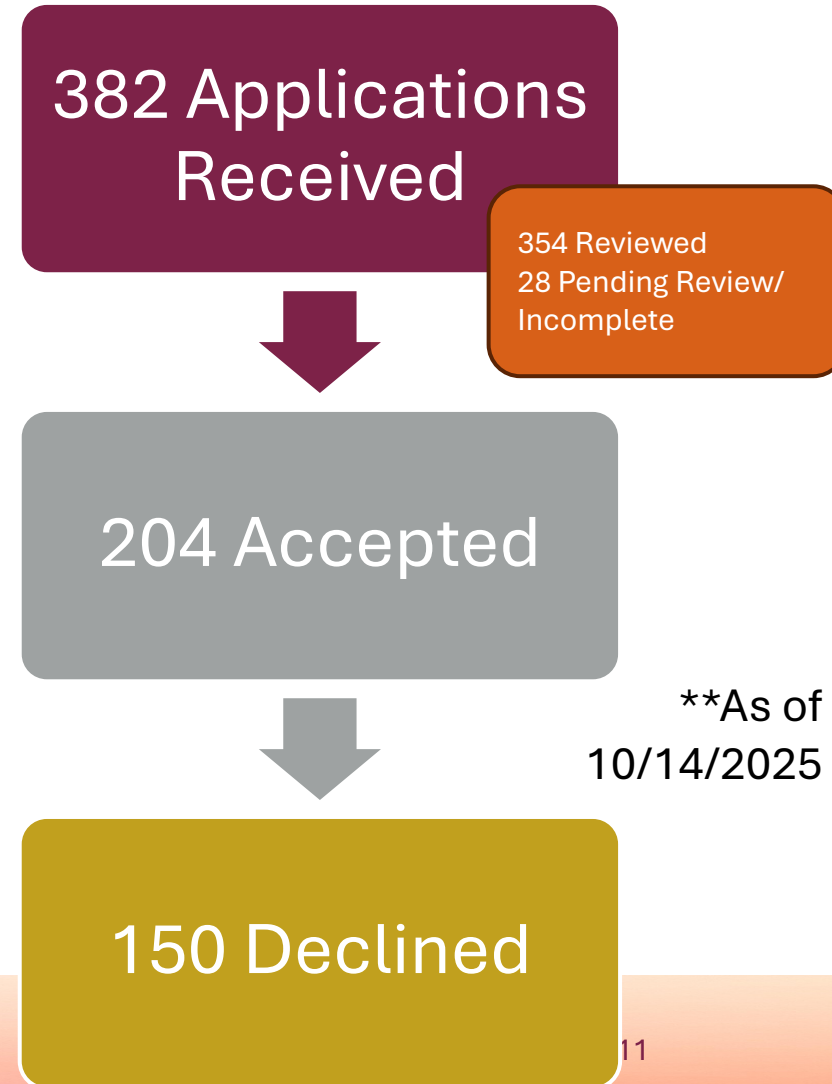
- Most patients cited in the literature carry two mutations (compound heterozygotes), neither of which are amenable to ASOs.
- To date: evaluated 5 patients in pre-submission
- Each Patient's mutations were evaluated in detail;
 - 2 patients carried 1 mutation that could be amenable to ASOs so recommended application
 - 1 has been submitted and accepted
 - Other patients aligned with expectations from literature

A Bias to say 'Yes': Application Review

Example: Declining Patient Application based on a Holistic Evaluation of Safety Risk

Example: Heterozygous Mutation in ATP1A3

- Patient's mutation causes a severe childhood neurological disorder, Alternating Hemiplegia of Childhood (AHC)
- Loss-of function mutations in this gene also known to cause a different pathogenic phenotype, Rapid-onset dystonia Parkinsonism.
- Extensive evaluation of patient's mutation including consultation with external experts and review at ATTC.
- Conclusion: While ASO therapy may be possible, n-Lorem felt that the risk was too great to pursue ASO therapy given the potential to cause a different disease related phenotype.





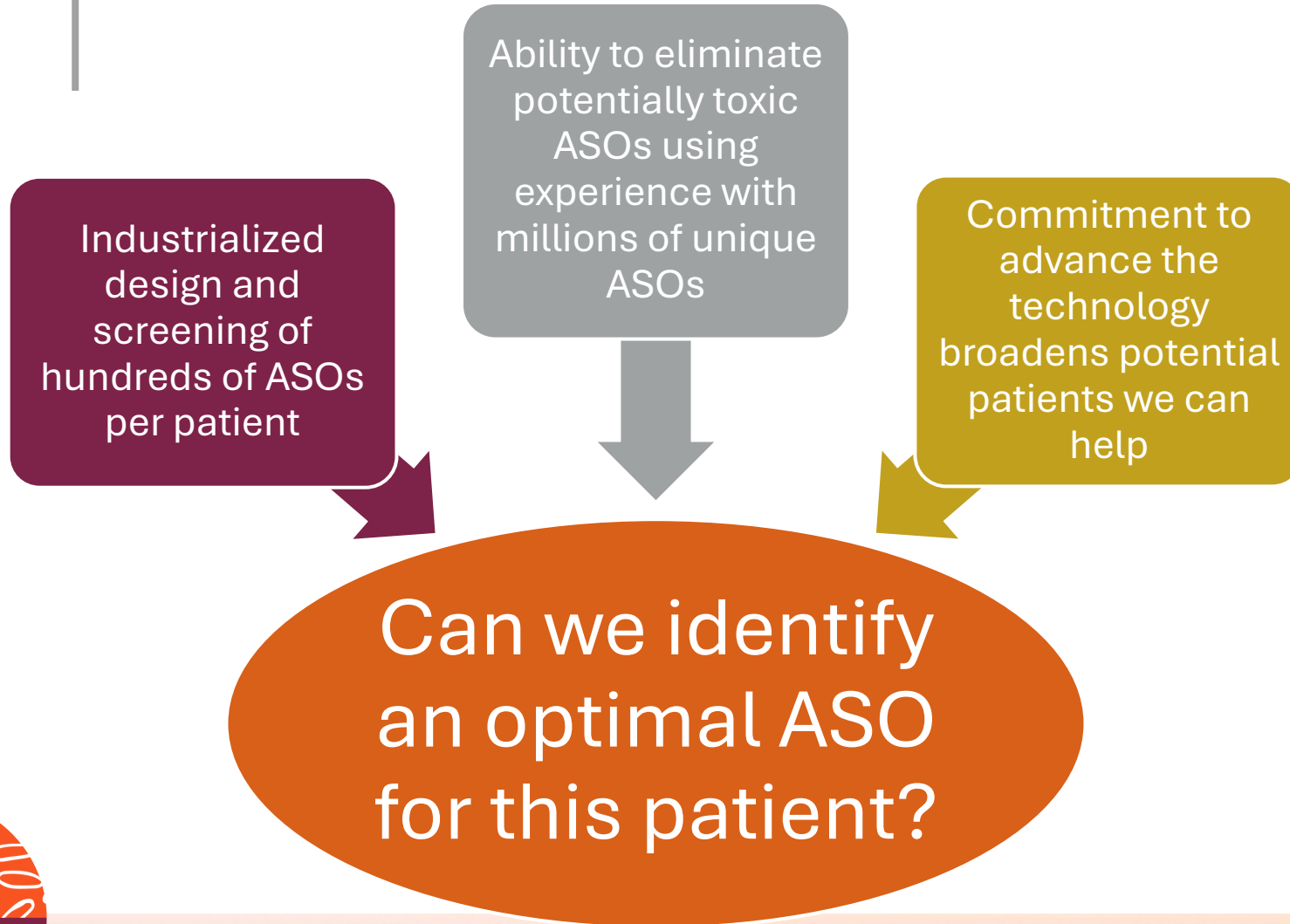
3RD ANNUAL

Nano-rare Patient Colloquium 2025



ASO Discovery and Development

A Unique **Combination of Innovation and Experience** Enables Efficient and High-quality ASOs for Every Patient



Expertise Required

Internal:

- Antisense technology
- RNA biology
- Bioinformatics
- Molecular and cellular biology
- Pharmacology
- Drug discovery and development

External expertise and committee:

- Extramural partners
- RMC

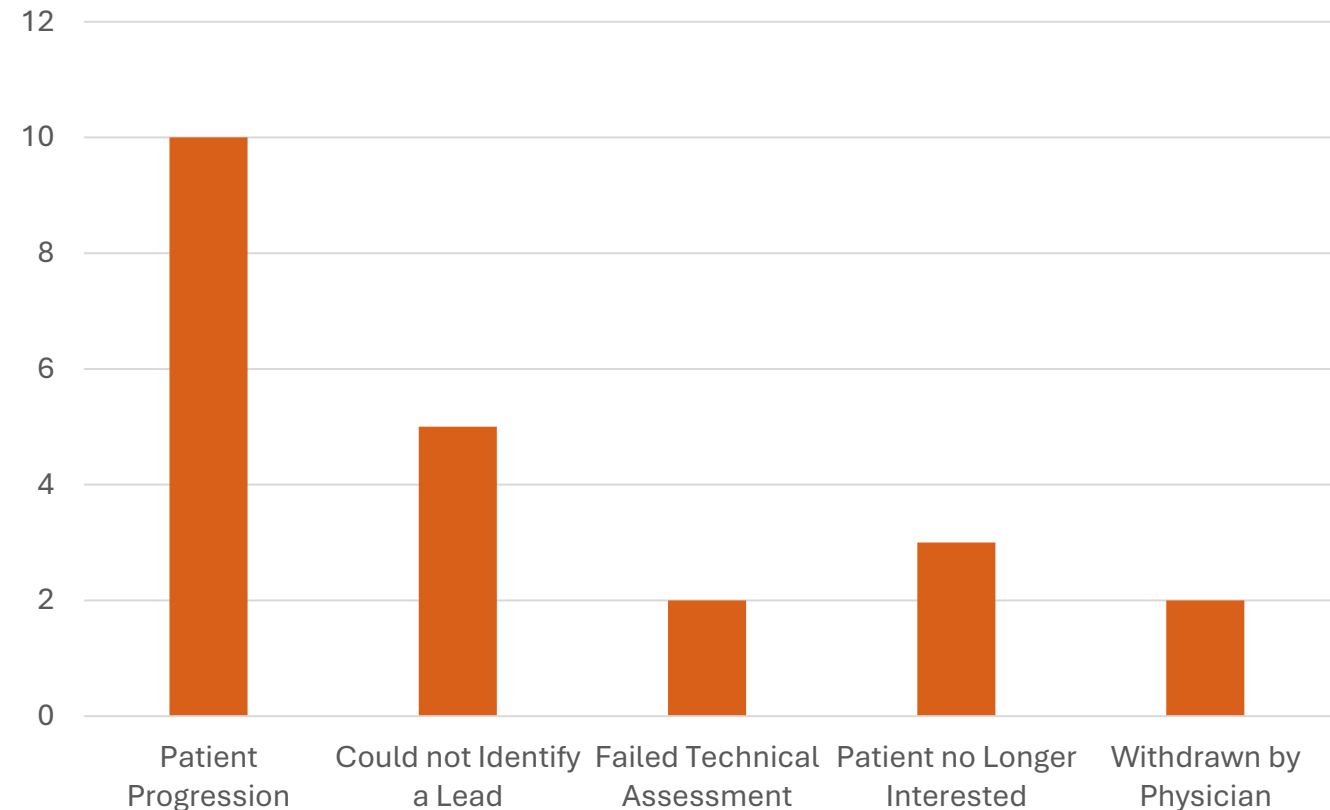
Unprecedented Success Rate Enabled by Industrialization and Deep Understanding of the Technology

- >15 patients' **ASO discovery and development data packages** or circumstances were reviewed at 15 RMC meetings since establishment of the committee in the past 22 months
- >5 **program challenges** were discussed and decisions made to pursue alternative path
 - Example: start non-allele selective, move to allele selective (or vice versa)
- **>90% of programs that progressed to GLP tox were successful in identifying an optimal clinical ASO**
 - The majority of each program costs are incurred during non-clinical development (GLP tox, manufacturing, sterile fill)

Nano-rare Patients Need Earlier Diagnosis and Treatment

- Almost 10% of patient programs were discontinued because the patient progressed during ASO discovery and development
- Patients need treatments sooner

% of Accepted Patients' ASO Programs Discontinued



n-Lorem Can Create Optimal ASOs that are Safe and Well-Tolerated

- The n-Lorem ASO Discovery and Development process based on the FDA guidance on Individualized ASOs **is necessary and sufficient** to identify optimal ASOs for the majority of patient ASO cases
- Observations from **successful patient programs** creates cumulative knowledge and data
- Observations from discontinued patient programs can inform future cases
 - Example: Small number of SNPs in several patients led to a novel approach to managing these cases



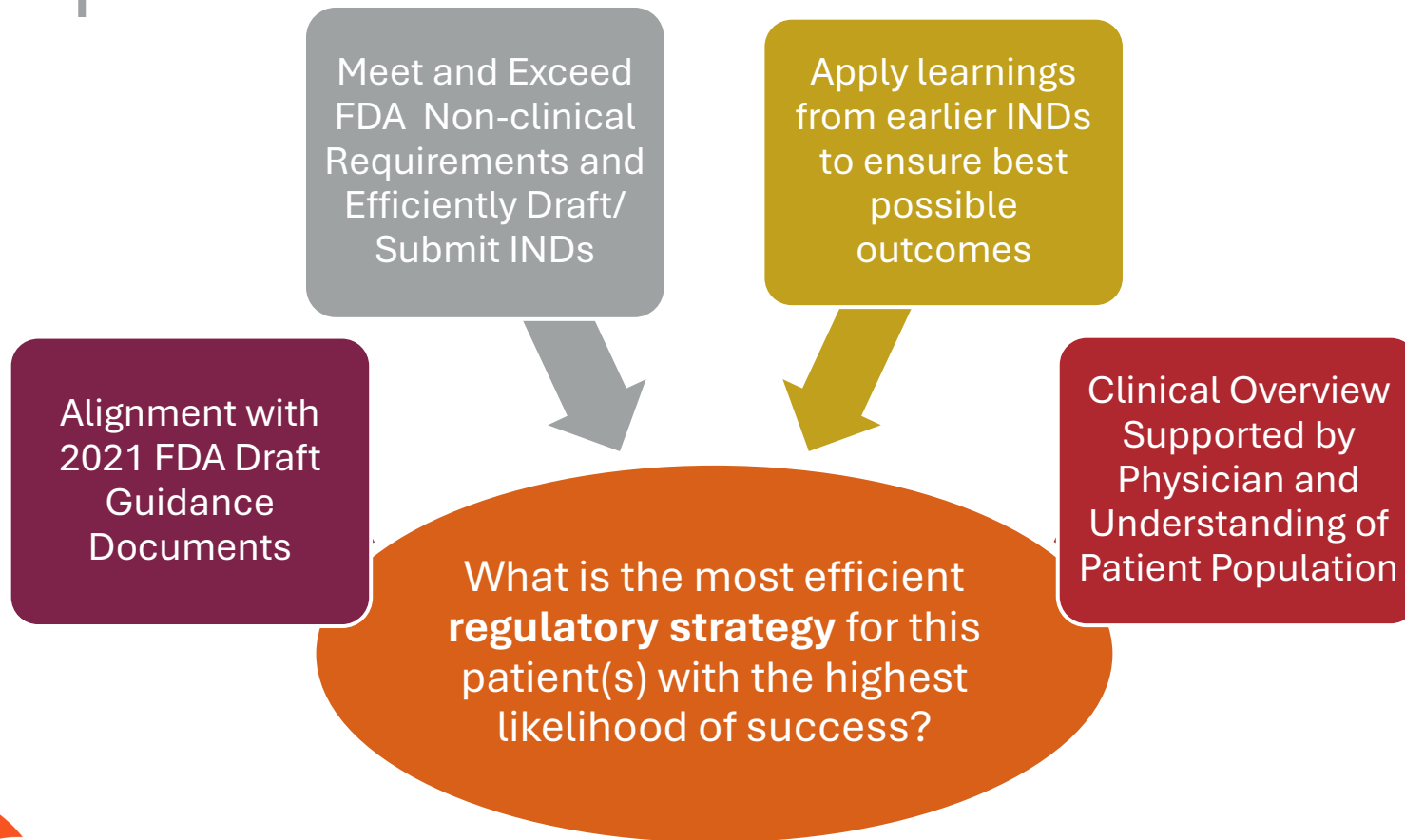
3RD ANNUAL

Nano-rare Patient Colloquium 2025



Regulatory Strategy and Authorization

Growing Portfolio of Success Across Four Divisions of FDA Builds Confidence and Efficiencies



Expertise Required

Internal:

- Regulatory operations
- Regulatory strategy
- Nonclinical
- Clinical

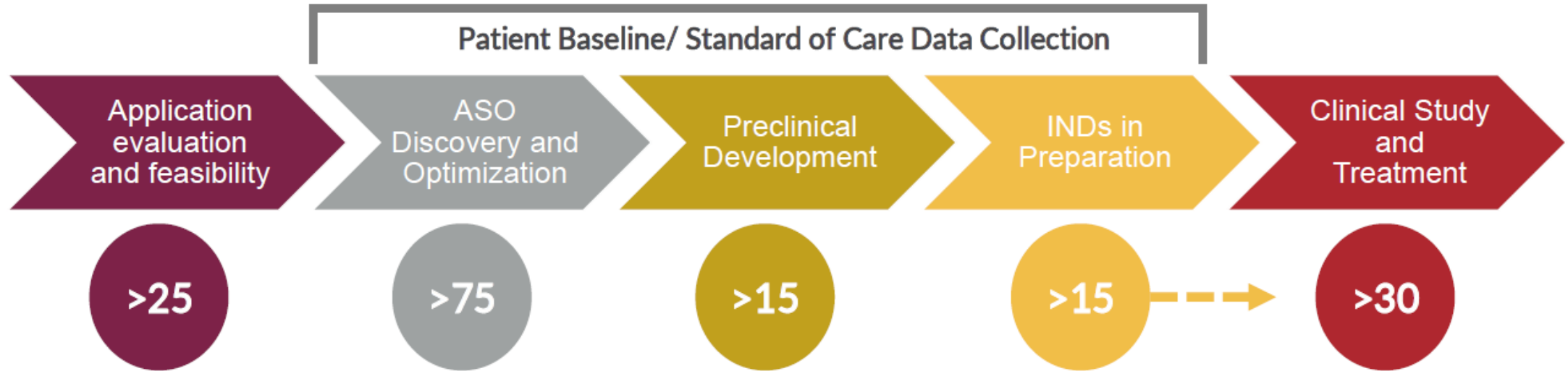
External expertise and committee:

- FDA

Regulatory Strategy and Authorization Protects Patient Safety

- **n-Lorem ASOs account for ~90% of the individualized ASOs used to treat patients today**
- **FDA Guidance is predicated by millions of unique ASOs** spanning different lengths, chemistries, modifications, sequences enable understanding of consequences of each
 - ~Nearly half a million patients have been treated
- n-Lorem provides a unique combination of **innovation and experience** to overcome unexpected scientific and nonclinical nuances specific to each target

Extraordinary Progress Towards Patient Treatment



>360 Applications Submitted to Date
>200 Patient-directed Drug Discovery Programs Accepted to Date
>35 INDs Submitted
4 Divisions of the FDA Supportive

Consistent Collaborative Engagement with FDA Enables Success Today

- n-Lorem Experience with the FDA has been **incredibly positive**
- n-Lorem has submitted and obtained authorization for **>35 Research INDs to 4 divisions of the FDA**
- Response times continue to be **within the expected review period of 30 days**
- n-Lorem recently **expanded our team** to accommodate the increase in scope and number of regulatory engagements

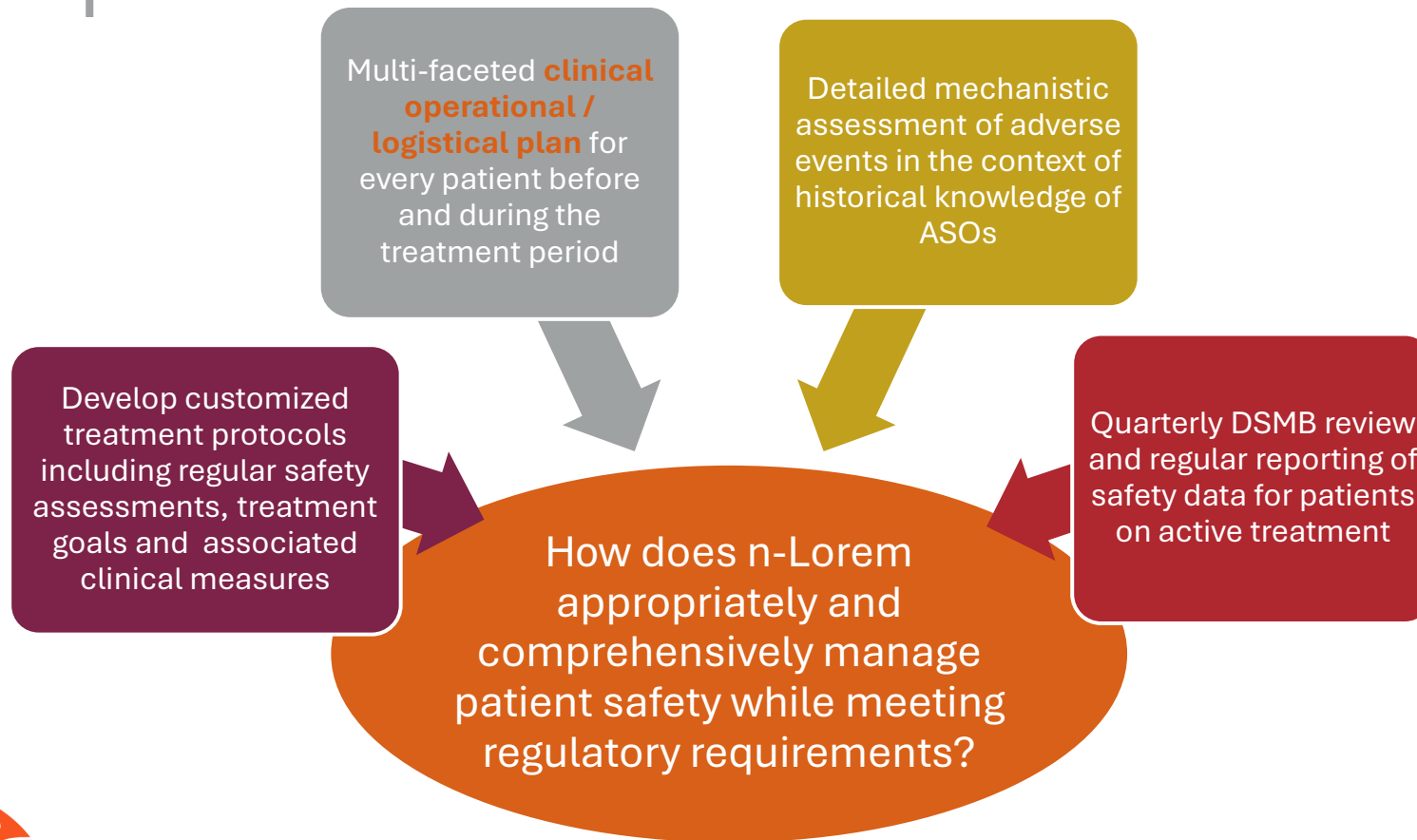


3RD ANNUAL
**Nano-rare Patient
Colloquium 2025**



Clinical Protocol Implementation

Professional Management of Parallel Processes Expedites Safe Treatment of Nano-Rare Patients



Expertise Required

Internal:

- Clinical development
- Clinical research associates
- Clinical data scientists
- Outcome assessments
- Antisense oligonucleotide clinical treatment
- Clinical trial execution

External expertise and committee:

- STAR
- IRB
- DSMB – Antisense; Medical; Clinical Trial Safety Monitoring

Clinical Development Metrics

- >40 STAR committee meetings during which physicians presented and discussed patient outcome assessments
- 37 protocols drafted and incorporated into INDs
 - All protocols approved by institutional IRBs
- **110,879 Data points collected in REDCap ***
- 8 Quarterly DSMB meetings covering datapoints on every patient on treatment at that time, and growing

* As of 10/15/25

Key Takeaways

- All treatment protocols include standard safety assessments
- Clinical efficacy is evaluated according to each patient's phenotype
- STAR Provides an external checkpoint to ensure each patient is assessed appropriately and that cross-physician and cross-patient learnings can be applied
- REDCap Data Collection successfully ties patient data across all programs to a compliant and centralized location to enable data aggregation
- The n-Lorem DSMB provides an objective sounding board to evaluate patient data and comment on safety concerns



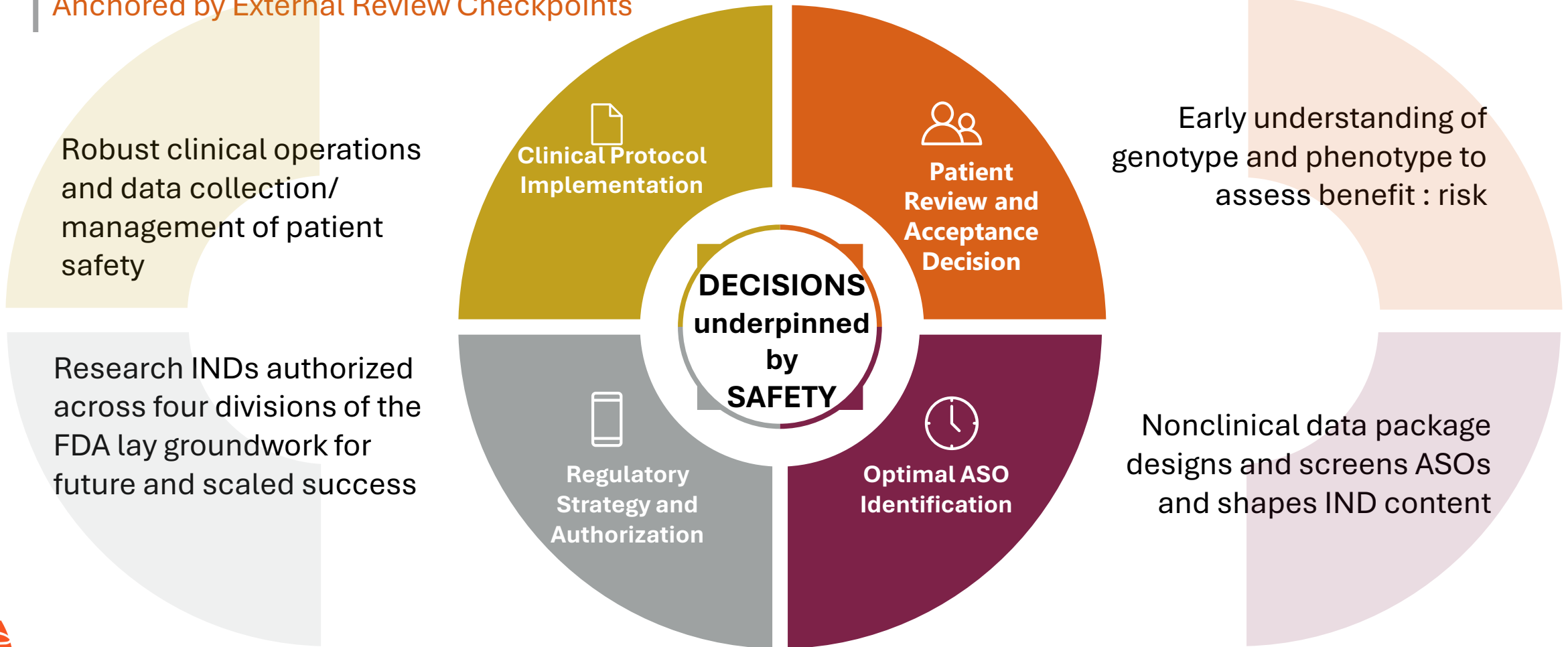
3RD ANNUAL

Nano-rare Patient Colloquium 2025

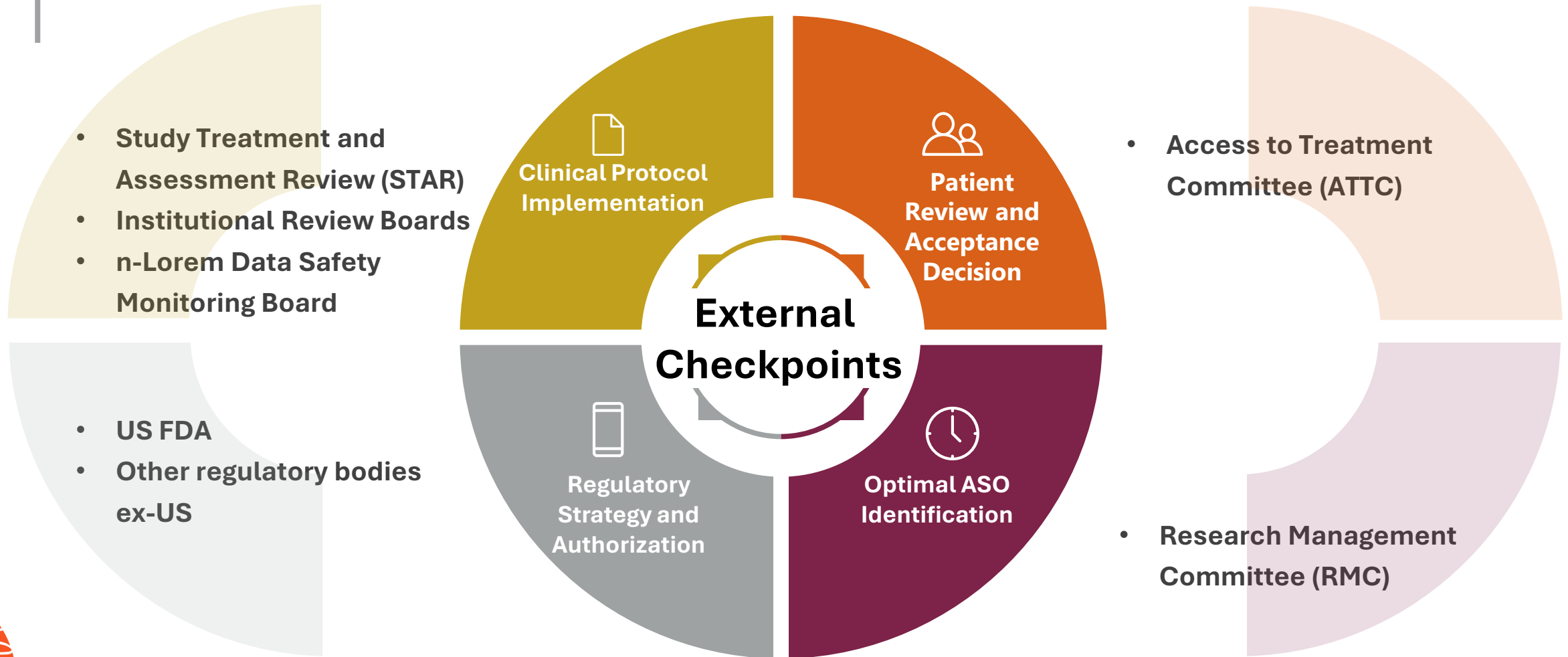
Conclusions

Key Decision Points Throughout the n-Lorem Process are Underpinned by Safety

Anchored by External Review Checkpoints



Extramural Committees Provide an *Additional* Layer of Review and Safety Checkpoint



Patient Safety is n-Lorem's Highest Priority

- Every decision - small and large - made throughout a patient's ASO program is important and is driven **to protect patient safety**
- **Metrics exemplify the scale** of the nano-rare patient need today that will continue to grow tomorrow
- Precision medicine means that learnings from each patient program can be applied in real-time
- **n-Lorem is creating safe and well-tolerated ASOs for the nano-rare**



3RD ANNUAL

Nano-rare Patient Colloquium 2025

Thank You