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Nano-rare Patient Colloquium 2025

Treating for Life: The Importance of Data

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Anchoring from our Morning Session: Clinical Data is the Central Tool for Individualized Patient Treatment

Treating an individual patient can lead to life changing outcomes



Powerful learnings stem from analysis of data across all nano-rare patients treated with individualized ASOs



Learning across patients with the same class of disease (ALS) is likely the only and most powerful way to accelerate treatments for future patients



n-Lorem's Data Philosophy and Approach

- For the first time in history, there is an **unprecedented volume of data** collected on nano-rare patients at n-Lorem which must be used to learn optimally.
- Data must be collected in accordance with the **highest quality and compliance** to meet current and potential future regulatory requirements.
- Data sharing is **non-negotiable** and **time-critical** to ensure that the data outcomes are interpreted and applied accurately.
- While baseline / early treatment data is critical, **long-term data are** of the utmost importance.
- **Concrete evidence** drives progress for nano-rare and healthcare for all.

Outline

- I. Defining the Data
- II. Implications of Data on Patients and Families
- III. Data Sharing
- IV. Lessons Learned
- V. Conclusions: Data as the Foundation of the Future of Nano-Rare



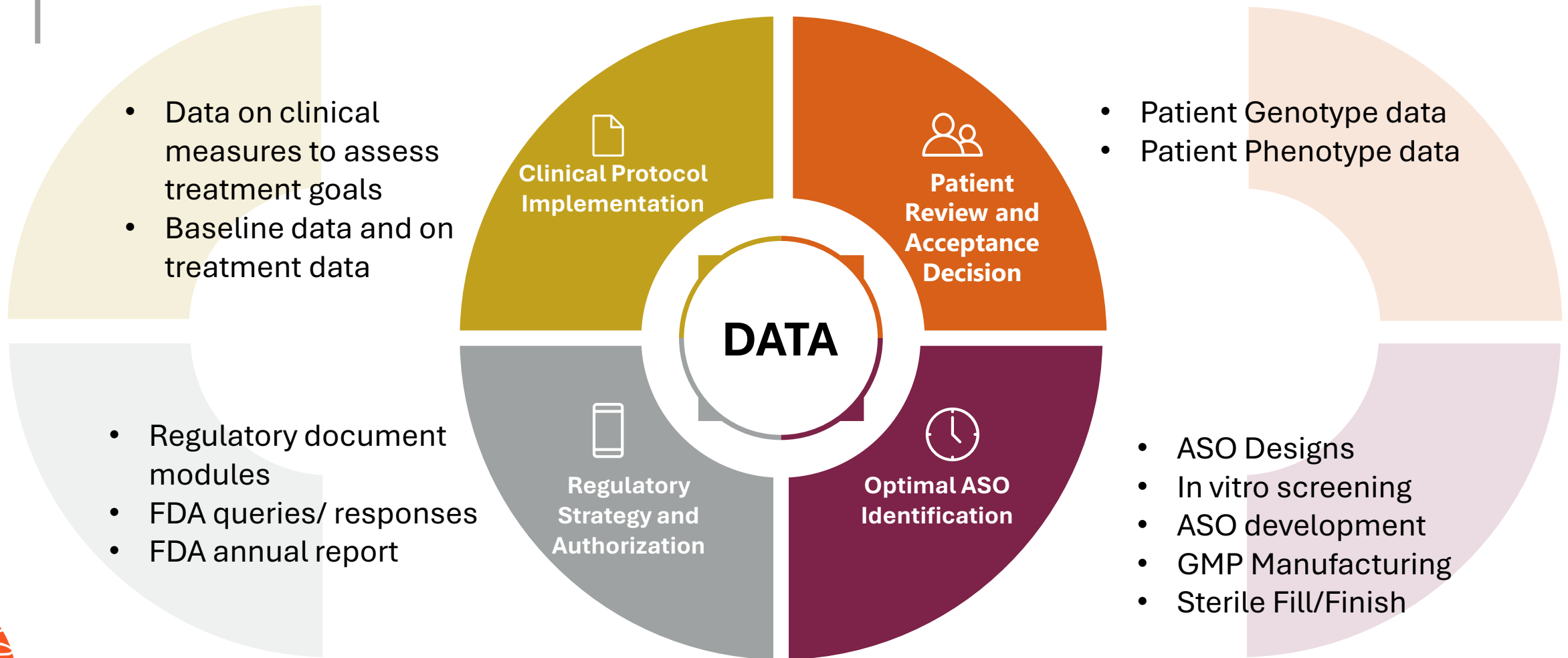


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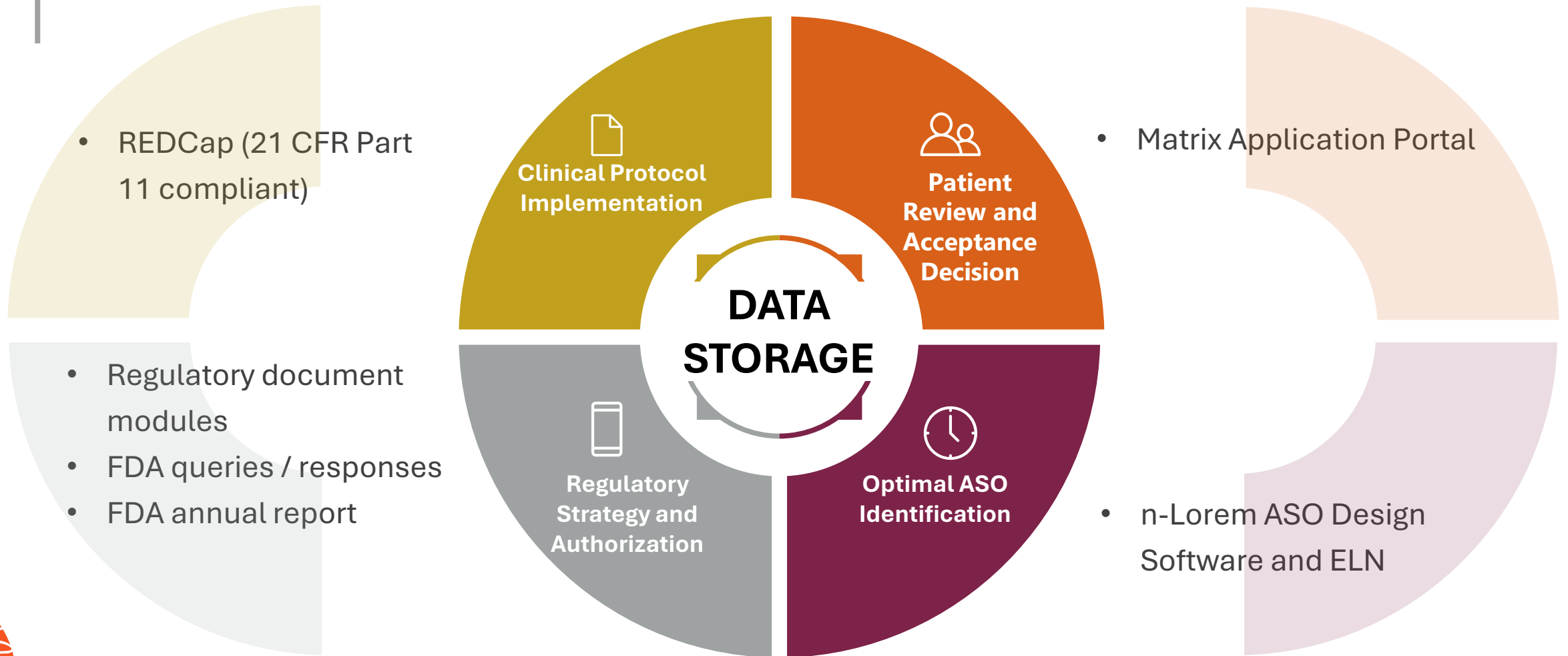
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I. Introduction: Defining the Data

Defining Data Drives Decisions Across the n-Lorem End-to-End Integrated Process



Data Storage and Compliance Across the Integrated Process



Benefit vs. Risk – The Core Lens

- Every decision made for a patient program at n-Lorem is driven by **benefit : risk** and is grounded by **data**.
- Benefit : risk
 - Drives research choices and patient decisions
 - Balances *what* we can do for a patient with *how* we do it safely.





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II. Implications for Patients and Families

From Individual to Aggregate: Maximizing the Value of Every Data Point

Patient-level Data

Evaluate
Benefit/Risk

Real-time
adjustments to
treatment
protocol

Cross-Subgroup Data

Optimize and
leverage data to
refine effort for
the next patient

Nano-rare Population-level Data

Compare, refine treatment approaches, molecular
mechanisms, technological and clinical outcomes assessments

Individual Patient Level Data will Enable Movement from Treatment as Research to Clinical Care

Patient-level Data

Evaluate
Benefit/Risk

Real-time
adjustments to
treatment
protocol

**Moving from
research to
clinical care**

Cross-Subgroup Data

Optimize and
leverage data to
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Nano-rare Population-level Data

Compare, refine treatment approaches, molecular
mechanisms, technological and clinical outcomes assessments

Driving a Change in the Healthcare Overall: A Heightened Focus on The Needs of Individuals

Individual Nano-rare Patients

Subgroup of Nano-rare Patients (i.e. ALS)

Nano-rare Population

Rare- and Common- Disease Populations

A Focus on Each Nano-Rare Patient: Acknowledging Differences While Leveraging Similarities

Potential for Aggregation:

- A treatment goal
- Clinical outcome assessments
- Severity at time of IND drafting
- Target gene
- SNP targeted by the ASO

Likely to be Unique / Different:

- Journey to Diagnosis and n-Lorem
- Concomitant medication profile
- Combination of clinical manifestations

Every Patient is Unique:

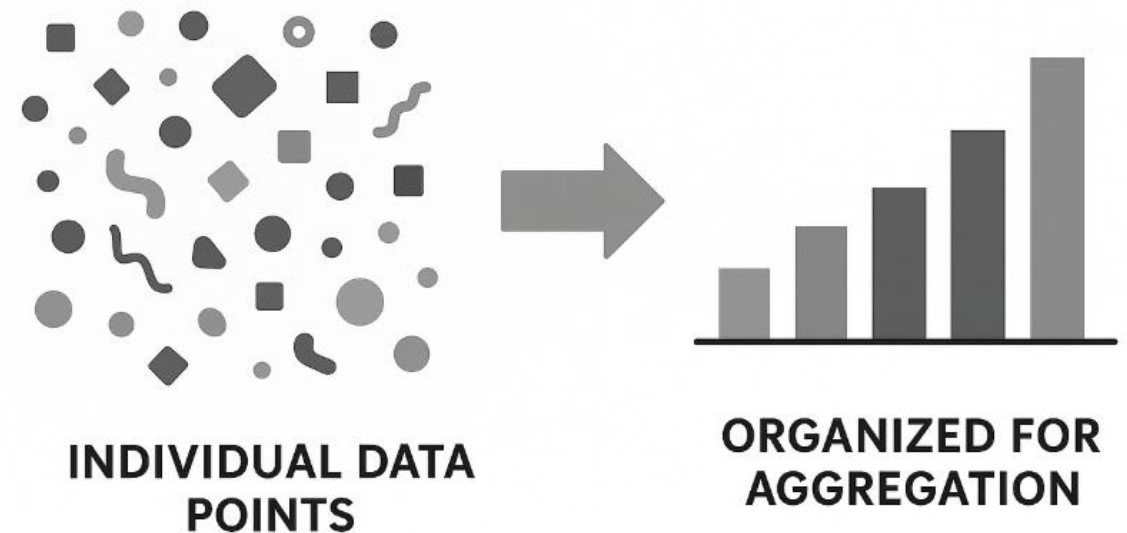
Patients with same mutation in can have variable phenotypes -
HNRNPH2 as an example

Patient	Age/ Sex	Shared Phenotype	Unique Phenotype
#1	7 yr/ F	Global developmental delay or intellectual disability	Seizures, autism, ADHD, hypotonia with spasticity, dystonia, cortical visual impairment, GERD and constipation with feeding difficulty and failure to thrive, self-injurious behavior
#2	7 yr/ F		Seizures, hypotonia with spasticity, cortical visual impairment, GERD with feeding difficulty and failure to thrive
#3	7 yr/ F		Seizure history, autism, ADHD, concern for cortical visual impairment , self-injurious behavior
#4	12 yr/ F	Behavioral or neuropsychiatric symptoms	Autism, cortical visual impairment, ataxia and dysmetria, hyperreflexia and ankle clonus, osteomalacia, chronic constipation
#5	29 yr/ F		Rett-like phenotype with regression and stereotypies, cortical visual impairment, abnormal gait, constipation
#6	21 yr/ F		Seizures, cortical visual impairment, osteoporosis
#7	21 yr/ F	Anxiety	Autism, renal tubular acidosis, dystonia, concern for cortical visual impairment
#8	42 yr/ F		Seizure history, autism, ADHD, self-injurious behaviors

Evaluating each patient independently allows n-Lorem to account for the uniqueness of the patients and to collaborate with each physician on customized treatment decisions

The Art of Meaningful Data Aggregation

- **Larger Dataset = More Robust**
therefore every assessment is important
 - Recognize the contribution of improving/
changing data collection methods
- Interpretation of **incomplete data** can be challenging
 - Makes participation in every protocol
assessment critical
- Document **quality and providence of the ASO** is a necessity to thoroughly differentiate causation of treatment effects



Two patients, One ASO: A Meaningful Impact on Communication



- Example: Susannah and Sloane, both treated with the first KIF1A ASO
- Data provide evidence of what we see in the video, in day-to-day life
- Capturing these moments as data informs clinical care

What This Data Means for Patients & Families

- Data collected today will not only help you but also the future of the nano-rare
- Data exemplifies n-LoRem's ability to discover, develop and provide individualized ASOs to nano-rare patients safely and equitably.





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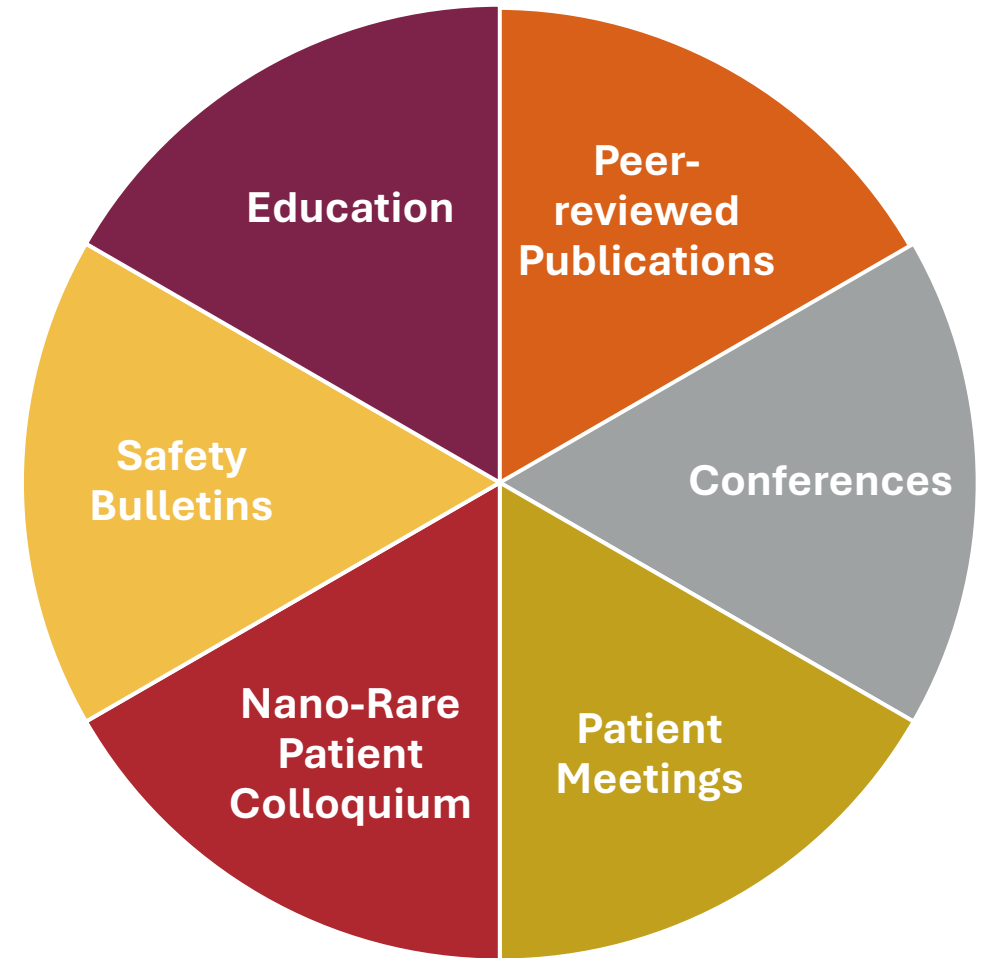
III. Data Sharing, Education and Information Flow

Establishing a Broad Knowledge Base for Researchers, Patients, and Families

- Given n-Lorem's role in nano-rare treatments, it is also our obligation and privilege to **ensure the community is educated** about a) what they need to know and b) what we are learning.
 - Includes rapid awareness of critical and relevant events such as safety observations
- Broad knowledge sharing **draws attention to the needs of nano-rare** which will be critical to inform policy or payer changes in the future

Why Publication Matters: Making the Data Count – Publishing & Sharing

- Critically important to n-Lorem:
 - Scientific rigor
 - Transparency
 - Objective peer review and validation
- Broaden scientific reach
- Share directly
- Prioritize open, accessible communication
- Additional knowledge sharing
 - Lessons in antisense
 - Podcasts
- Encourage collaborators to share broadly



Right Data, Right Audience, Right Time

Recent Publications in High-quality Journals

Nucleic Acid Therapeutics

Addressing the needs of patients with ultra-rare mutations one patient at a time: the n-Lorem approach

Harnessing novel technology and a non-profit model to meet the needs of patients with ultra-rare disease

TheScientist
EXPLORING LIFE, INSPIRING INNOVATION

Meeting the needs of patients with ultrarare disease



Trends in Molecular Medicine
A Cell Press journal

nature biotechnology

- A call to arms against ultra-rare diseases
- A way forward for diagnosis of patients with extremely rare genetic mutations

A toxic gain-of-function variant in MAPK8IP3 provides insights into JIP3 cellular roles

JCI insight

Med

Evaluating human mutation databases for 'Treatability' using personalized antisense oligonucleotides,

Splice-modulating antisense oligonucleotides targeting a pathogenic intronic variant in adult polyglucosan body disease correct mis-splicing and restore enzyme activity in patient cells



Nucleic Acids Research

nature medicine

- Antisense oligonucleotide therapy in an individual with KIF1A-associated neurological disorder
- Personalized antisense oligonucleotides 'for free, for life' - the n-Lorem Foundation
- Antisense oligonucleotide as a therapeutic approach in amyotrophic lateral sclerosis



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IV. Lessons Learned

Defining (and Refining) the Treatment Goals and Clinical Measures

- **No two patients are the same** although they can be / are being treated with the same drug
 - Proper management of long-term treatment is critical
- **Evaluation of treatment response will vary** as a function of each specific patient and their treatment goals— and that's expected
- Data helps us refine dosing, timing, and expectations in **real-time**



Achieving a 'Maintenance' Dose is Not Straightforward and is Affected by Many Elements

- Severity of disease at treatment start is highly variable
- Rate of progression is not clearly defined
- Pediatric patients grow, mature and change intellectually and emotionally
- Each type of assessment varies in terms of precision and optimal time to measure
- Concomitant meds and other health events (ex. Covid, stomach bug, breaking a leg) complicate
- Disease specific considerations that are built into each protocol:
 - Example: Neurodevelopmental assessments require a longer time before we can determine benefit



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V. Conclusions: Data as the Foundation of the Future of the Nano-Rare

The n-Lorem Commitment to Sharing High-Quality High-Fidelity Data



- Ensuring external awareness of our data sharing priority is critical as a non-profit
- Purposeful, proactive and meaningful engagement across all stakeholders in the nano-rare space can have massive benefits
 - Ensuring alignment with new physicians and sites
 - Level-setting expectations from all parties
 - Maximizing strengths of one another to meet patients' needs
- Questions? Interested in collaboration? Ask us!

A Comprehensive Approach to Knowledge Sharing

- We have paved a **new path** for healthcare for the nano-rare
- **Everyone involved is a pioneer** - knowledge and learnings should be shared broadly to ensure each contributor has the information they need to participate fully
- n-Lorem is the only organization that has the **integrated capabilities and associated datasets** that span from patient review / acceptance through ASO discovery and development, to regulatory approval and treatment

Changing Healthcare for the Nano-Rare

- Data tells the story of individualized treatments
- Proper and robust data collections helps us measure, improve, and scale
- We are establishing the basis of n of 1 clinical science and broadly understanding health and disease — together
- And we're committed to sharing everything we learn
- **Every single data point matters,
...and n-Lorem is making sure each one counts.**



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Thank You!



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