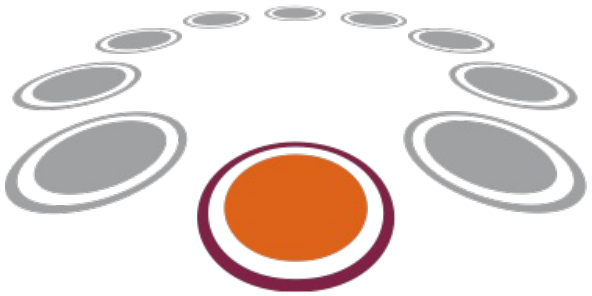

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Guidance for n-Lorem Quality Processes

Overview Of n-Lorem Quality Processes To Identify An Optimal ASO

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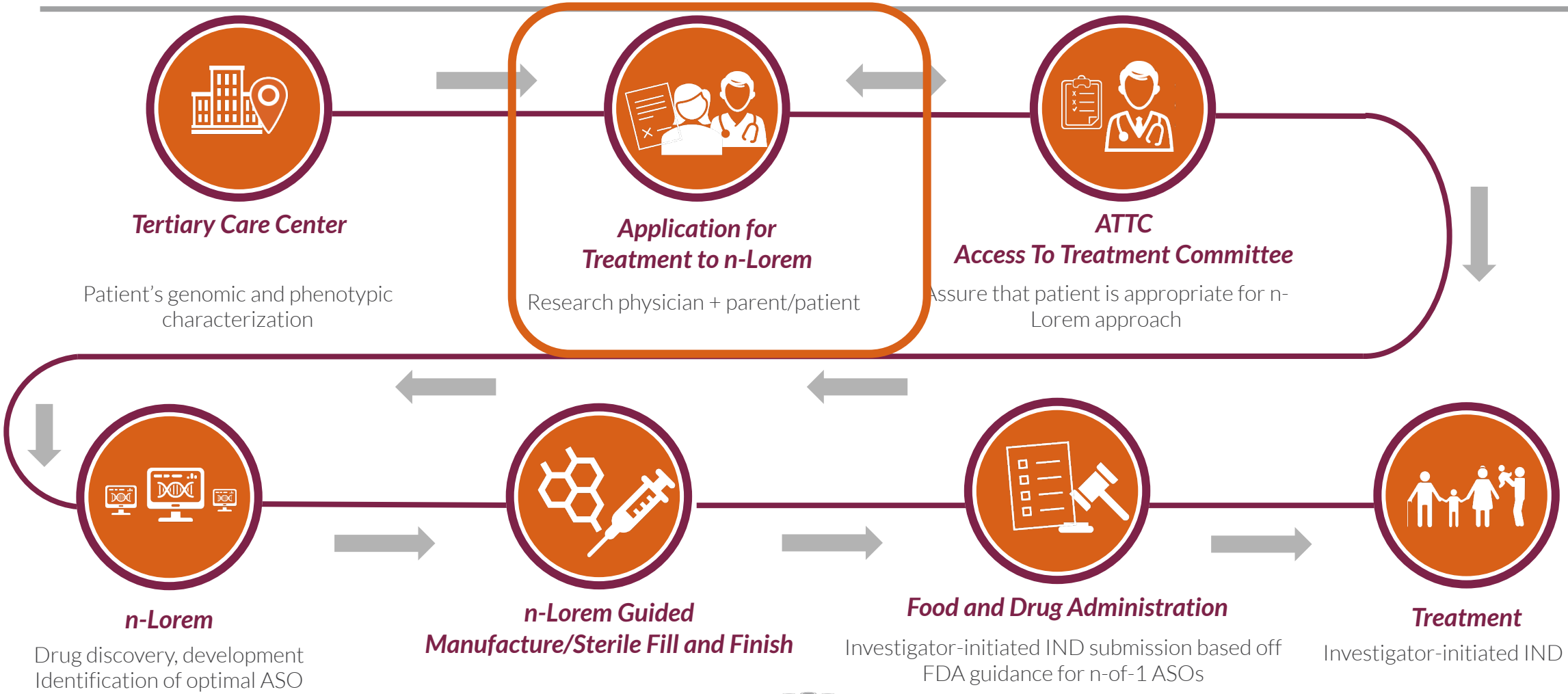

Online Application Portal Enables Benefit/Risk Decision (Sample)

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Patient Submission

n-Lorem is focused on creating individual treatments for patients in the United States with ultra-ultra-rare diseases caused by genetic mutations that affect approximately n1-30 patients in the world. Diseases or conditions with broader patent populations are likely more suitable for treatment by other non-profit or for-profit entities, which we encourage you to explore with your physician before submission.

☐ By clicking this box, I have read and understand the guidelines. *

Guidance for Submission

Strengths and limitations of ASO technology:

ASO technology is validated, versatile, effective in many organs at low doses, deliverable by many routes of administration, and active both systemically and locally.

Currently, n-Lorem is focused on these organs and routes of

SECTION 1: SUBMITTER INFORMATION - (*REQUIRED)

Name of Submitter *

First Name | Last Name

Relationship to Patient: * ○ Patient ○ Physician ○ Guardian ○ Other

Patient Name *

Parent/Guardian Name

(If not same as above.)

Submitter Contact Information:

Phone Number

Area Code - Phone Number

Email

example@example.com

May we contact the patient's primary physician?

◉ Yes
○ No

Online Application Portal Enables Benefit/Risk Decision (Sample, continued)

SECTION 2: INFORMATION ON THE PHYSICIAN WHO WILL BE LISTED AS PI UNDER INVESTIGATOR SPONSOURED IND

Physician's Name *

First Name Last Name

Specialty

Institution *

Qualification of treating physician including recent CV

Browse Files

IRB Contact

(Not required for submission)

Host Institution Approval for Investigator Initiated IND

(Not required for submission)

SECTION 3: GENERAL PATIENT INFORMATION - (*REQUIRED)

Age * Weight * Height *

Sex *

Male Female Undisclosed

Patient Location *

City State / Province

Please Select

Country

Physician/Institution evaluation

- Is there a physician and institution capable of treating and monitoring this patient for the rest of the patient's life?
- What experience does the physician and institution have with treating patients or conducting investigator led INDs?
- Does the physician or Institution have experience with regulatory agencies?
- What is the institution's funding situation?

Online Application Portal Enables Benefit/Risk Decision (sample, continue)

SECTION 4: PATIENT HISTORY

Brief description of patient history including primary organs affected.

Predicted Disease Trajectory *

- ○ Rapidly Progressing
- ○ Slowly Progressing

Primary Goal of Therapy *

What Medications Have Been Tried?

List Current Medications

SECTION 5: GENETICS

Gene Name

Gene ID

Predicted Consequence of Genetic Change *

- ○ Gain of Function
- ○ Dominant Negative
- ○ Partial Loss of Function (haploinsufficiency)
- ○ Total loss of Function
- ○ Unknown

Supporting Data, Including Model Organism Data

Organs Affected (Check All That Apply) *

Liver	Kidney	CNS	PNS
Skeletal	Integumentary	Cardiovascular	Pulmonary

Note: Currently, n-Lorem is focused on these organs and routes of administration:

Liver: Subcutaneous
Lung: Aerosol
Kidney: Subcutaneous
Eye: Intravitreal
Central Nervous System: Intrathecal

Patient evaluation

- What are the signs and symptoms of the patient and the progression of the disease?
- What outcome is expected from treatment?
- How severe is the disease?
  - ASO development takes about 18 months, so estimate of whether patient will be amenable after that time is important
- Is it only developmental?
  - ASOs cannot address signs and symptoms if they aren't progressive
- What organs is it affecting?

Validated Routes of Administration for PS ASOs

SYSTEMIC	LOCAL
Intravenous	Intravitreal
Intramuscular	Intrathecal
Subcutaneous	Aerosol
Oral	Rectal

Crooke ST et al., ***NAR***, 2020, 48(10):5235-5253; Crooke ST et. al., (2020) ***JACS*** 142(35):14754-14771, Crooke ST et al., Nature Review Drug Discovery, 2021, 1-27, Crooke ST et al., JBC, 2021. 296:1-39; Crooke ST et al., Biochem Pharm, 2021 Jul;189:114196.

Potency of Modern ASOs in Select Organs

Organs	Routes
CNS	IT
Liver	SQ
Lung	Aerosol
Kidney	SQ
Eye	Intravitreal

Online Application Portal Enables Benefit/Risk Decision (Sample, Section 5 continued)

SECTION 5: GENETICS

Genotype (Patient sequence & Reference sequence)

Browse Files

Genetic Diagnosis

Browse Files

Relevant Family History

Browse Files

Estimated number of patients with same genetic diagnosis. ex: 23

Estimated number of patients with same genetic change. ex: 23

Current and prior participation in experimental studies.

Browse Files

(IF AVAILABLE)

SECTION 6: INFORMATION TO SUPPORT ANTISENSE DRUG DISCOVERY

Summary of Gene Function

Availability of patient derived cell lines (fibroblasts, lymphocytes, etc.o

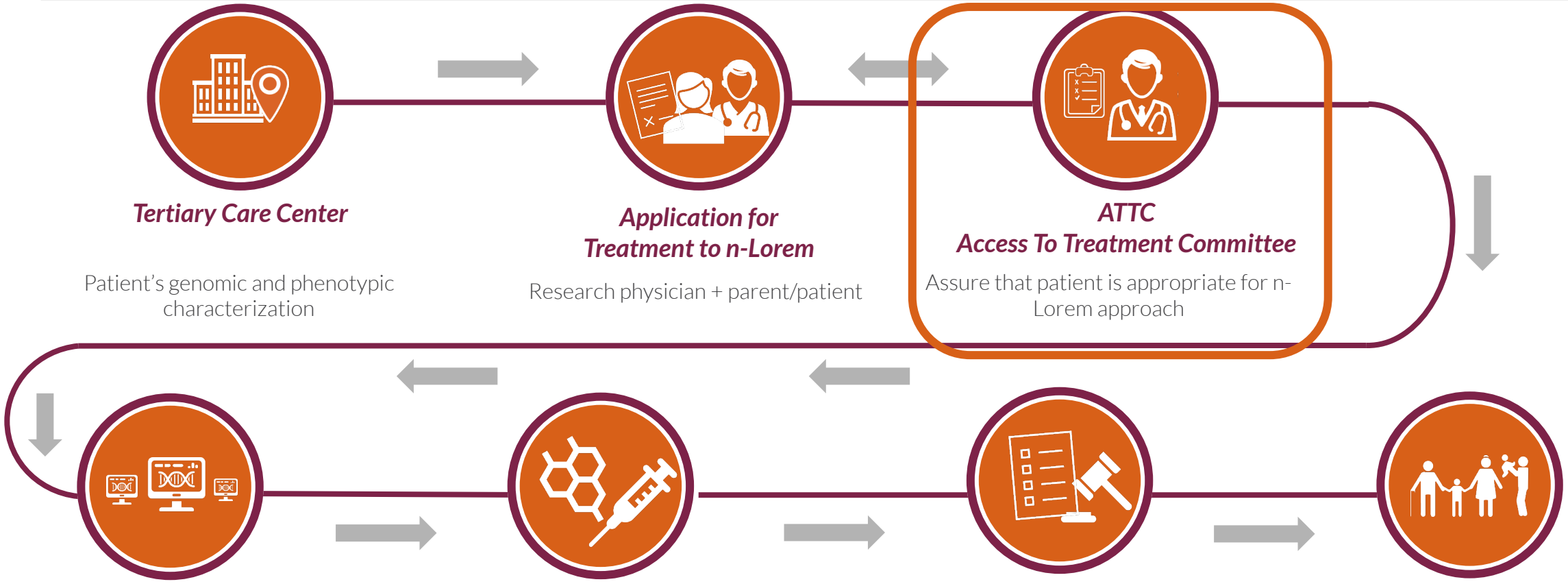
Availability of Mouse Models

Submit

Mutation evaluation

- Evaluation of genetic report
  - How many pathogenic SNPs identified in what genes?
    - Are they heterozygous, compound heterozygous, homozygous
  - What is the molecular consequence of each?
    - How are the mutations affecting gene expression of the target and downstream effector expression?
  - What is the functional consequence of each mutation depending on what's known about the normal gene function?
    - Toxic gain of function, loss of function (partial or complete), dominant negative (Uniprot/OMIM/decipher/varsome etc.)
    - ASOs cannot address a total loss of function
- Is there a clear genotype/phenotype relationship with a single pathogenic mutation?
  - What is the evidence that a single mutation is causing the signs/symptoms/progression?
  - What is the evidence that expression of the target gene is causing disease progression?
    - Is it expressed in the adult?
    - Are there any publications in animal models to confirm pathogenicity and signs and symptoms?
    - Has any work been done to modulate expression of the gene to show benefit with proposed mechanism?

Overview Of n-Lorem Quality Processes To Identify An Optimal ASO



Tertiary Care Center

Patient's genomic and phenotypic characterization

Application for Treatment to n-Lorem

Research physician + parent/patient

ATTC
Access To Treatment Committee

Assure that patient is appropriate for n-Lorem approach

n-Lorem

Drug discovery, development
Identification of optimal ASO

n-Lorem Guided Manufacture/Sterile Fill and Finish

Food and Drug Administration

Investigator-initiated IND submission based off FDA guidance for n-of-1 ASOs

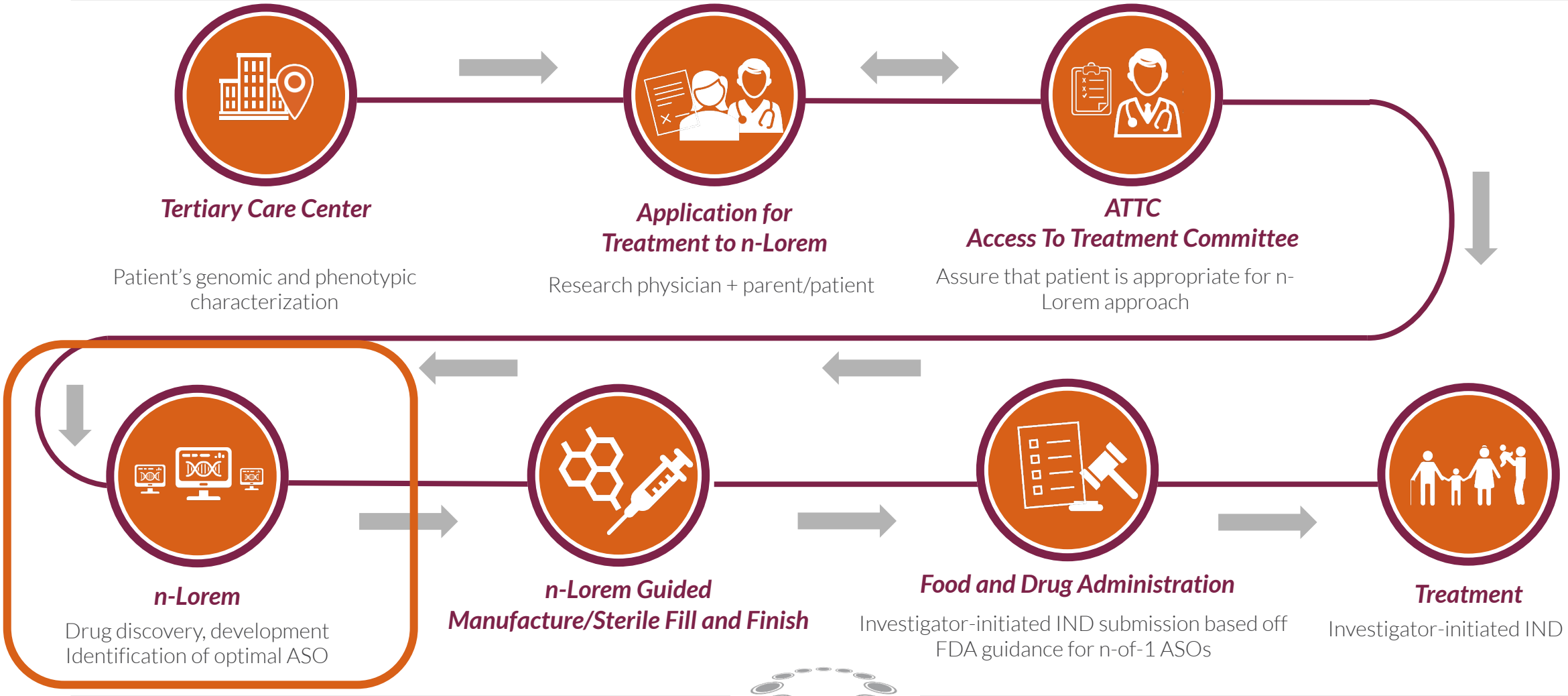
Treatment

Investigator-initiated IND begins

N-Lorem applications undergo complex risk/benefit decision-making to decide whether n-Lorem can help each patient

- An optimized treatment application on n-Lorem website
  - Genotype
  - Phenotype
  - Primary, secondary, and exploratory treatment goals
- Rigorous assessment of genotypic and phenotypic evidence that an ASO approach is appropriate
- Assessment of the urgency of intervention
- Presentation of patient to Access To Treatment Committee (ATTC)
- Final decision made by n-Lorem Executive Team

Overview Of n-Lorem Quality Processes To Identify An Optimal ASO Once Accepted into n-Lorem



Expectations and Accountabilities Following Acceptance into n-Lorem

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- Discovery and develop individualized ASO
- Provide ASO for free, for life
- Establish and uphold quality models
- Provide clinical research support for:
  - Regulatory process
  - Protocol development
  - Set-up for data collection

n-Lorem and Investigator

- Develop treatment protocol synopsis and protocol
- Determine baseline assessments and collection
- Data collection (CRFs)
- Patient safety

Investigator

- Ensure institutional support
- II-IND holder
- Meet IRB requirements
- Consent patient for treatment periods of program
- Collect and share data with n-Lorem

Partnering to accelerate patient's treatment

- If needed for patient's program: Sequencing data and cell acquisition (MTA)
- n-Lorem will support meeting **institutional requirements for investigator-initiated studies**
- n-Lorem will **provide the physician quarterly updates** on progress of patient in n-Lorem process
- Physician begin to draft **natural history evaluation and data collection plan** to establish with n-Lorem team
- n-Lorem team **will initiate program kick-off** when discovery team has identified ASO leads for your patient
  - Project leader/ clinical operations support
  - Regulatory operations leader

Overview Of n-Lorem Quality Processes To Identify An Optimal ASO

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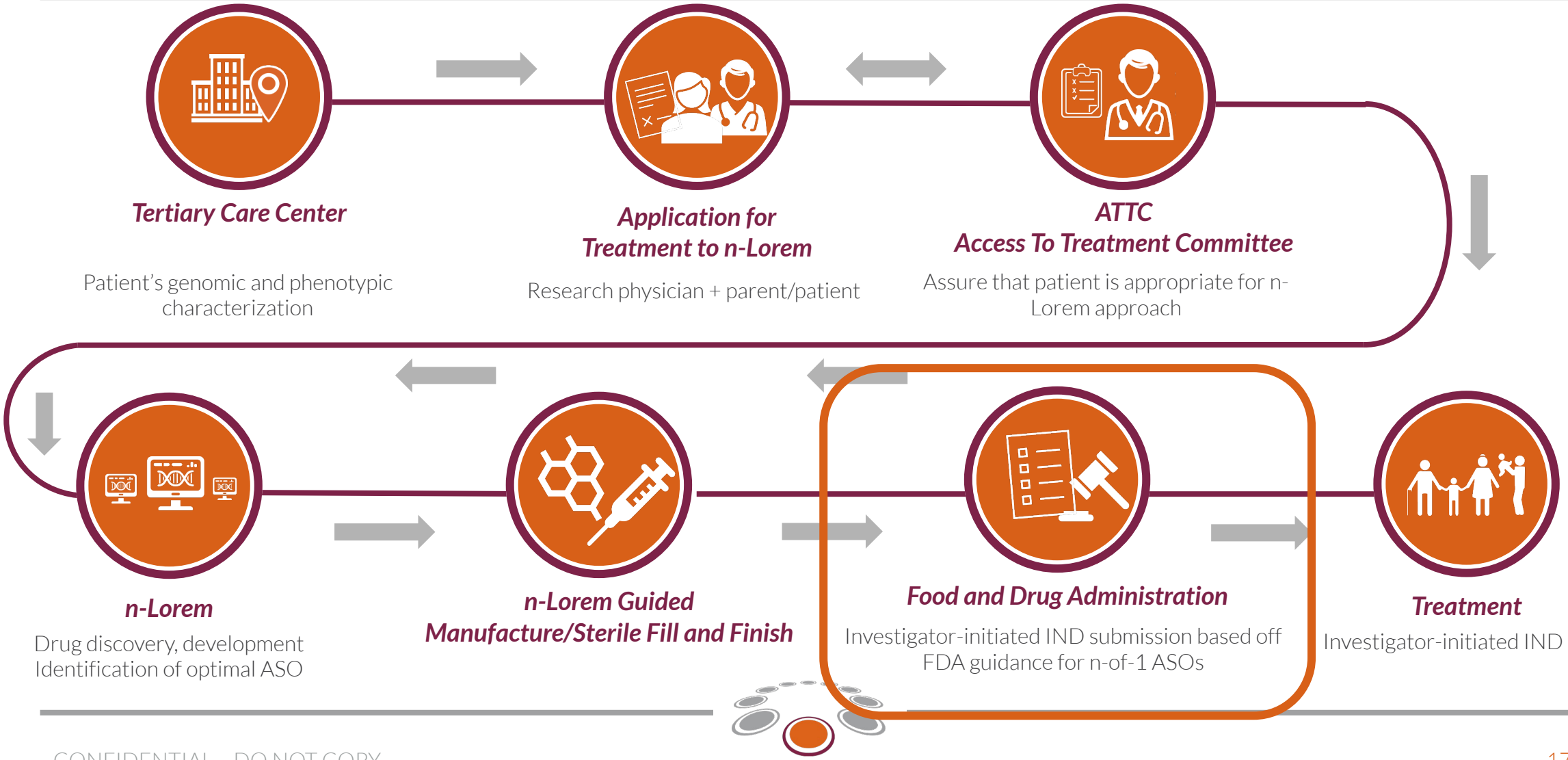

Regulatory Support Established - ASO Guidance Issued

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- FDA response to n-Lorem concept supportive
- n-Lorem posed questions that require policy decisions, but progress toward policies evident
- In the meantime, experience facilitating ASOs for individuals provides real-life guidance
- Initial FDA guidance for ASO for patients with diseases caused by ultra-ultra-rare mutations: Jan. 4, 2021
- Pre-clinical requirements: Detailed guidance April 2021
- CMC guidance Dec 2021
- Clinical guidance Dec 2021