Physician FAQ

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1. What type of clinical study are n-Lorem patients treated under?

    - Experimental ASO treatments discovered and developed by n-Lorem are administered to n-Lorem patients according to a patient-specific clinical protocol under a Research IND held by n-Lorem.
    - These are not traditional clinical trials, and each IND and clinical protocol is customized to the individual patient.
    - n-Lorem does not provide funding or a clinical trial budget to physicians or institutions to cover the costs of treatment administration, physician time, pharmacy costs, and outcome assessments.

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2. Who will submit my patient's IND?

    - n-Lorem drafts >90% of the content of and submits all Research INDs, with the principal investigator being defined on the application. This reduces the regulatory burden on each site and streamlines submissions and FDA interactions for all n-Lorem patients.
    - Each physician will be expected to provide clinical content for the IND related to the patient and to sign off on the clinical protocol.
    - n-Lorem will manage all communication with the FDA for the lifetime of the IND including adverse event reporting and annual updates.

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3. What are my responsibilities as a physician for working with n-Lorem?

    - Each n-Lorem program is a collaboration between the physician who is requesting a treatment for their patient and n-Lorem. There are many important commitments for each physician who submits an application to n-Lorem and is interested in treating their patient with an n-Lorem therapy:

i. Provide a cell line from your patient to n-Lorem for use during our drug discovery process. This may be fibroblasts or iPSCs depending on the gene target and anticipated expression levels in different tissue types. Physicians are responsible for paying for any costs with generating the cells and shipping them to n-Lorem. No work will commence in our laboratory until the cells have been received.

ii. See your patient routinely in the clinic and provide updates from your visits (including clinic notes) to n-Lorem.

iii. Regularly meet with the n-Lorem team to provide updates on your patient's clinical status and receive updates on the program's progress to share with your patient.

iv. Communicate discovery and development updates directly to your patient and manage their timeline expectations using program specific information provided to you by n-Lorem. n-Lorem remains blinded to patient's identities and does not provide updates to patients.

v. Work with n-Lorem to establish individualized treatment goals for your patient and present your proposal to an outside committee for endorsement.

vi. Collect robust data using agreed upon outcome assessments both before and during treatment and share this data with n-Lorem.

vii. Contribute clinical content to the IND, obtain IRB approval for the study, and consent your patient.

viii. Work with your institution to secure adequate support and funding to be able to treat your patient.

ix. Administer treatment to your patient via the route of administration specific to your patient's disease indication (ie. Intravitreal, intrathecal, or subcutaneous).

x. Manage adverse events in collaboration with n-Lorem.

- You will not be provided any financial compensation from n-Lorem for your involvement in treating your patient with an n-Lorem ASO.

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4. What are my institution's responsibilities for working with n-Lorem?

- Your institution will be expected to enter into a Treatment Agreement with n-Lorem. Drug cannot be shipped to your site until this agreement is executed.
    i. There is no study budget provided as part of the Treatment Agreement because n-Lorem studies are not traditional clinical trials.

- Your institution will be responsible for funding all costs associated with administering the treatment to your patient and performing clinical outcome assessments.
    i. n-Lorem will provide the drug supply, for free, for the life of the patient as long as you as the treating physician deem a favorable benefit:risk ratio.

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5. **If n-Lorem does not provide funding for drug administration, how do institutions cover these costs?**

- Many physicians / institutions cover these costs by:
    i. Billing to insurance
        1. Insurance coverage varies widely based on the provider and state of coverage.
    ii. Using philanthropic or research funds
    iii. Submitting grants
        1. If you have a grant in mind to submit for, n-Lorem is happy to help provide necessary content to you and / or draft a letter of support.

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6. **How do I receive a copy of the clinical protocol?**

- There is no protocol that applies to all n-Lorem patients. Each clinical protocol is customized to the unique phenotype of each patient and all outcome assessments will be tailored to your patient in collaboration with n-Lorem. However, we can provide an example schedule of assessments based on the anticipated route of administration to provide a high-level overview of the type of content our protocols typically include.

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7. **How do I nominate a patient for consideration?**

- Applications are submitted through the n-Lorem portal "Matrix".
- Account requests are reviewed and granted once n-Lorem has confirmed each submitter's understanding of their roles and responsibilities and the institutional infrastructure available to support our unique n of 1 study environment.

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8. My patient resides outside of the United States, can I submit them for consideration?

- At this time n-Lorem can only treat patients who reside in the US. Applications for international patients will not be accepted although this may change in the future.
- We encourage you to check back frequently to the n-Lorem website for updates on our efforts to expand beyond the United States.

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9. How long is the application review process?

- Applications are reviewed in the order received. The completeness of each application upon receipt and timeliness to answer any follow-up questions or requests for additional documentation influence our review timelines. In general, a decision on each application is made within 1-3 months of application receipt.

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10. My patient was accepted to the n-Lorem program, now what?

- n-Lorem will initiate a unique ASO discovery and development program for your patient once all necessary data and materials have been received. The process to execute the necessary legal agreements and obtain the required data and cell material for each program can take between 3-12 months depending on the institution.
- Once all materials are received, our rigorous discovery and development process takes a minimum of 18 months. However, this timeline can vary substantially based on the gene target of interest and complexity of the program. n-Lorem will provide routine updates to you along the way which can be shared directly with your patient.
- It is important to note that for some programs we will not be successful in identifying a therapy for the patient.
- In some cases, an ASO may be available for your patient already. In these situations, we will communicate directly with you regarding the regulatory strategy for treatment.

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11. **What materials and data are required for my patient's program to move forward from being accepted to becoming an active ASO discovery and development program?**

    - Depending on the planned ASO strategy, your patient's program may require long read whole genome sequencing (WGS) data. n-Lorem has a vendor who can consent your patient and provide the sequencing at no cost to you or the family if your institution cannot generate this data in-house. Requirements for sequencing will be communicated directly to you and you will be responsible for connecting your patient with our sequencing provider, as needed. Once sequencing data is available, the n-Lorem sequencing provider will send the data directly to n-Lorem for analysis.
    - Most programs in our laboratory require patient cells for our experiments, and we cannot move a program forward in our laboratory until all required cells have been received. The cell type needed will be dependent on the anticipated expression levels of the gene target of interest. Requirements for the cell type will be communicated directly to you, and you will be responsible for coordinating and funding sample collection and generation of any necessary cell lines. Once a Material Transfer Agreement (MTA) is executed, we will arrange for shipment of the patient cells to n-Lorem.
    - Before a program can move forward in our laboratory, a technical review is required to determine if ASO design will be feasible. Once sequencing is completed, n-Lorem scientists will evaluate the patient's genetic information to determine if ASO design is possible. n-Lorem will update you when this review has been completed.

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12. **What type of data am I responsible for collecting during my time collaborating with n-Lorem?**

    - Once the technical assessment for your patient's program is complete, n-Lorem will work with you to define the individualized treatment goals and relevant outcome assessments that will be used to measure those goals. These goals and assessments will drive the framework of your patient's individualized clinical protocol.
    - It is expected that you will collect at least 1 year of data pre-treatment using the agreed upon outcome assessments.
    - Each treatment protocol will also require at least 1 year of on study data collection.
    - Data on the clinical outcome assessments according to the protocol is required to be collected as long as the patient remains on treatment with the n-Lorem ASO unless a different strategy is discussed and agreed with n-Lorem.
    - All data will be shared with n-Lorem via a REDCap database that will be built specifically for your patient by n-Lorem.

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13. What is the route of administration and frequency of dosing for CNS patients?

- n-Lorem ASOs for CNS indications are administered intrathecally. Dosing typically occurs at Day 1, Month 1, Month 3 and quarterly thereafter. At the first dose and each dose escalation (4-5 visits in the first year of treatment) an overnight hospital stay is required for observation. Once we have reached a maintenance dose on a quarterly schedule, the observation period becomes 6 hours vs. overnight. The dosing regimen will be precisely defined for each patient's ASO.
- As a non-profit organization, n-Lorem does not provide clinical trial funding to sites to cover the costs of drug administration and hospital stays.

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14. What is the route of administration and frequency of dosing for ophthalmologic patients?

- The route of administration for ophthalmologic indications is intravitreal with dosing typically occurring every three months, however it will be precisely defined for each patient's ASO.
- As a non-profit organization, n-Lorem does not provide clinical trial funding to sites to cover the costs of drug administration.

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15. What is the route of administration and frequency of dosing for kidney or liver patients?

- The route of administration for systemically delivered ASOs is subcutaneous with dosing typically occurring monthly, however it will be precisely defined for each patient's ASO.
- As a non-profit organization, n-Lorem does not provide clinical trial funding to sites to cover the costs of drug administration.
