openNHS Manifesto

Manifesto – *a published verbal declaration of the intentions, motives, or views of the issuer. A manifesto usually accepts a previously published opinion or public consensus and/or promotes a new idea with prescriptive notions for carrying out changes the author believes should be made.*

Mandate for OPEN Natural History Studies

Natural History Studies (NHS) are generally pre-clinical and do not give commercial advantage to sponsors. Therefore, they should be collaboratively defined, implemented and executed, and *all* study results, including raw data should be openly shared as soon as practical to optimize research and minimize the impact on the patient community. This is especially true when the study is invasive, painful, risky, or otherwise inconvenient for the participants. These issues are magnified in rare diseases where the patient populations are small.

Essential characteristic of an openNHS:

We acknowledge that a Natural History Study is required to provide a baseline to compare proposed treatments and therapies and are often used as part of a regulatory or clinical trial application. Further, we note that experts in specific rare diseases are more rare than the patients themselves and are often not found in the participant's home city.

- NHS study designers, implementers, data users, and the study participants recognize that the NHS is not for competitive advantage nor in its purest form does it provide clinical value to the participant. Rather a NHS is a vehicle to compare the viability of a potential therapy, as well as means to better characterize and understand the disease.
- Study designers should openly collaborate to define and capture as broad a range of NHS data as practical, including that which might be needed in the near term for a clinical trial or an IND as well as that which would enable better understanding of the disease.
- Most researchers anticipate the development of another generation of more effective or viable therapies after the current therapy is approved and implemented – the longevity and breadth of openNHS studies should help to facilitate this future research. Therefore, openNHS study designers should consider both current and future therapy development as they define and implement an openNHS.

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- Study designers and users from both for-profit and not-for-profit (including academic and disease advocacy organizations) should come together to expedite and maximize the study design to gather as broad a data set as possible along with strategies to engage the disease community in the study. This is especially true where the community is small and/or pending therapies could potentially forever modify the natural course of the disease due to wide acceptance.

- Collaboration is not only about data; collaboration should also include NHS study costs, operational issues, patient access & engagement, and optimal use of physical and human resources.

For the participant, the ideal openNHS study sites have these characteristics:

- NHS study sites become more than data collection vehicles that only benefit researchers by committing to becoming knowledgeable about the disease with the goal to provide clinical value and improved quality of life to the study participants.

- NHS study sites become regional centers of knowledge about the disease with connections to key disease experts in other regions and/or countries.

- NHS study sites expand the patient visit to include regular informed clinical evaluation and support. These extra visit expenses are, in most cases, billable and reimbursable as clinical support so these extra services will not be a financial burden on the study.

- The sites make referrals to, and suggestions about, care strategies and resources. The sites actively become a resource to the participant's medical care team in their home city to improve participant quality of life and care.

- Study sites consider and address the psychosocial and medical effects of the disease on both the individual participant and his or her family.

- Study collaborators, including advocacy organizations, should collaborate to create an environment at study centers where study site staff is engaged and educated about the disease by assuring resources are made available to the study site staff. This may include facilitated training, online resources, and establishing a communication channel with a remote disease expert.

- Participating in an openNHS requires that collaborators look beyond their current schedule to anticipate their future needs, and may require a contribution of efforts that is out of synch with particular project, however, the power of an openNHS is in working together to achieve a set of collaboratively

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defined goals and results that may be larger or superior to those any one researcher could define or implement.

- Clinical recommendations are provided to individuals and families in a culturally competent manner, which may include: language, educational level, and appropriate media.

With regard to the study data, the ideal openNHS study has these characteristics:

We acknowledge that publishing and IP rights are an integral part of the current research paradigm. This has a direct impact on data ownership and access. Effective openNHS collaborations will respect the needs of the individual collaborators, typically by a limited time protection of data from public release, after which the data becomes open to all.

- Data is gathered with long-term collaborative use as part of initial study design, data capture methods, data management, and data storage/access.
- Access to raw data, over the long term, is more valuable for ongoing and future research than summarized and published data. openNHS data sets facilitate access to raw data.
- An openNHS study can run effectively with global participation and retrospective data set integration as long as harmonization of methods and assessment standards is addressed.
- Study designers should consider clinicians might wish to contribute to the data set by reporting ongoing clinical visit data right alongside the more structured NHS data. This data may be directly input into the NHS system or may come as exports from, or links to, other data sets.
- Study designers should further consider study patients, non-study patients, and their caregivers might also wish to contribute to the data set resulting in patient reported data residing alongside more structured NHS data. Again, this might be via direct input or may be via export from, or links to, other data sets.
- Long term data management and IRB supervision should be considered in the study design and supervision documents with particular note taken of data destruction clauses, consent, flexibility for data use by future researchers, use of data from deceased patients, and a facility to re-consent participants.
- Beyond publishing and derived IP rights, data ownership should be made clear when a disease openNHS is launched with strong consideration to public or

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patient ownership with ongoing management of the data defined by the collaboration leadership.

With regard to the costs and longevity of an effective openNHS:

We acknowledge the costs of defining, launching, managing, operating, and providing for longevity of an openNHS exceed that of a single historical standalone closed study, however, it is our belief that over the long run, a single well defined and managed collaborative openNHS will be far more cost effective, provide access to broader and therefore more insightful data, facilitate and speed overall disease understanding, and be readily accepted by regulatory agencies while being more respectful and directly useful to the study participants and the patient community overall.

- openNHS requires the collaboration of those interested in a particular disease. These collaborators should include industry, academia, government researchers, disease advocacy and support organizations, and key disease experts.
- openNHS collaborations require contribution and pooling of physical, human, and financial resources. These resources should be overseen by study leadership committee.
- Often, different collaborators will contribute differing amounts and types of resources to different aspects of the study. It is critical that all collaborators be active contributors in some way and that all parties be transparent about their roles and contributions.
- A disease specific openNHS will probably function best under the leadership of several collaborators whose role will be to insure value, viability, and longevity of the collaboration and the data set.
- Collaborators should acknowledge and recognize a goal of openNHS is to facilitate data access in the future by researchers who were not involved in the gathering of the initial data set. It is quite appropriate that future researchers make financial contributions to the longevity of the data set via reasonable data access and usage fees, however, the principles of openNHS specifically prohibit the making of a profit off of the access or use of openNHS data.

Purpose and status of this document

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This manifesto is presented as a draft document to spur creative thinking and discussion. It is our desire to create a formal document as an outcome of the June 24th meeting of current MLD collaborators.

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