Fortrea

NATURAL HISTORY STUDIES

Harnessing the power of real-world data to drive more effective decision making in oncology clinical trials

In 2019, the United States Food and Drug Administration (FDA) released a document that demonstrated the changing attitudes to, and the growing importance of, natural history (NH) studies in drug development. The document provided guidance on the use of NH studies in rare diseases with the view to helping drug development organizations respond to an unmet health need; although each rare disease affects fewer than 1 in 200,000, there are around 7,000 different rare diseases and together they affect around 1 in 10 Americans.[1] Similarly, the European Medicines Agency (EMA)[2] and Japanese Pharmaceuticals and Medical Devices Agency (PMDA)[3] have also issued their own guidance on the use of real-world data to inform clinical trials, particularly with rare disease in mind, but also in the wider context of other diseases, particularly cancer indications.

By releasing guidance, regulatory bodies have highlighted the importance of using real-world data, via registries, retrospective data analysis or prospective observational studies, to track diseases in the absence of trial-specified intervention. This data can be translated into a deep understanding of the disease, its response to current therapies and the surrounding variables that correlate with its progression and outcome. By harnessing real-world evidence, clinical trial development, design and execution stages can all be improved, translating into tangible benefits, such as increased patient engagement, more favorable outcomes, development efficiencies and regulatory expediency.

This article explores the field of NH studies, explaining what they are and how they can be used to build faster, more efficient, patient-centric trials with a better chance of success and approval, both for rare diseases and the wider drug development market.

KEY TAKEAWAYS

NH studies draw on retrospective data from registries, diagnostics and patient records, as well as prospective observational studies

This information is used to track diseases in the absence of trial-specified intervention from randomized clinical trials and considers the frequency of the disease, its evolution and its current treatment

These detailed studies help drug developers understand diseases, their progression and responses to current therapies, which helps researchers identify the available market for a drug, as well as the patients who would be most suitable for a clinical trial

In turn, this helps developers design and execute more efficient and more complex, adaptive trials with better dose selections and better patient allocation

This leads to better trial outcomes, including:

- Increased patient engagement
- Equal socioeconomic access to trials
- Smaller, more efficient trials with fewer placebos
- Larger numbers of patients accessing active drugs
- More accurate data
- More successful outcomes
- Faster regulatory review

The untapped potential of real-world data

In the simplest terms, NH studies draw on real-world data collected from previous studies, diagnostics information and patient records to track the frequency, evolution and features of a disease as it progresses without trial-specified intervention. Since many diseases already have established treatment protocols, this ongoing and sometimes evolving treatment can be factored in as part of the NH study.

Epidemiological in nature, NH studies can help organizations explore disease genetics and patient demographics, as well as the treatment and concomitant modalities that are already associated with the current management of the disease in the real world. NH studies can cover a wide landscape of data and insight and are hugely varied, determined by the nature of the drug in development, the trial stage and its requirements.

Studies can be focused on:

- **Retrospective data** – Often the starting point for early stages of drug development, retrospective data can include existing patient information and medical records, diagnostic information, the results of previous related studies and other expert-driven data
- **Prospective data** – These are new studies that aim to track the disease into the future to gain further insights not provided from current data or to generate specific information that might act as a comparator arm for a proposed trial. Although these studies can take longer to run and require recruitment and medical observation, they can provide standardized results that mirror a clinical trial more closely
- **Cross-sectional studies** – These involve sampling disease progression across a cohort and observing the range of disease severity within the group. This data can be particularly useful for early-phase trials or to establish trial recruitment potential
- **Longitudinal studies** – These observe a cohort over time to allow a detailed understanding of a disease's progression, its prognostic variables and perhaps the manifestation of different subtypes. Although more resource-intensive than cross-sectional studies, longitudinal data provides a more comprehensive picture of a disease
- **Primary and secondary sources** – All NH studies can draw on primary or secondary data or a mixture of both depending on the nature of the study, the kinds of insight required and whether the data needs to be retro- or prospective

By mining vast, existing disease data, identifying gaps where further insight is needed and combining this with clinical trial data, it is possible to draw meaningful conclusions about the disease progression and its prevalence within a wider population. NH analysis is used to identify patient populations for clinical trials and gain insight into the wider market for a drug, providing the necessary information to design more effective, patient-centric trials that involve the right stakeholders at the right time. By understanding the disease profile and patient outcomes, organizations can design and accelerate trial outcomes, expediting the delivery of effective therapies to the market.

Putting the patient at the center of clinical trials

Critically, NH studies provide a deep understanding of a disease and how it progresses—at the patient level in the real world. Data, such as age, diagnosis indicators, tumor or disease subtypes, genetic markers and demographics, together with current treatment plans, can be amalgamated to provide a clinical development plan that contains a greater degree of real-world understanding and more realistic outcome assessments. This real-world grounding and evidence-based planning help generate a more patient-centric trial model[4] that can lead to better recruitment, retention and perhaps to more accurate outcomes.

Even in some of the most promising drug development pathways, a relatively low number of patients respond to trial treatments. A recent report showed that only 10%-50% of people respond to treatment with new immuno-oncology checkpoint inhibitor drugs[5] and another study on cancer patients in the U.S. suggests that this number may sit at the lower end of this range at around 13%.[6] NH studies based on retrospective data can help trial managers and clinicians allocate patients to trials and treatments more effectively with the view to improving these success rates. Using patient population and disease progression data, as well as more specific information, such as symptoms and predictors, trial managers can better gauge which patients might benefit from engagement in a trial. With this greater level of understanding, NH studies might also help with dose selection.

Identifying cohorts and ensuring substantial population sizes can also be a considerable challenge in clinical trials. By using NH studies to identify patient advocacy or disease-specific support groups, a greater number of patients can be identified and screened. This process is particularly important for rare diseases where patient cohorts can be particularly hard to identify or where early prognosis is needed. Coupled with a greater understanding of current treatment protocols and the efficacy of existing care, smaller trials can be used to reach the primary endpoint, making for a more efficient and timely trial.

Establishing relationships with treatment centers is also important. By identifying high-quality, trusted medical establishments, NH studies can help improve retention rates, and future studies can build on this success.

It is widely documented that socioeconomic and geographic biases exist when it comes to accessing clinical trials, with deprived patients underrepresented in cancer trials.[7] By exploring the wider demographic and socioeconomic profile of a patient cohort, trial managers can gain a deeper understanding of the target population and ensure that equal access is given to all patients who could potentially benefit from lifesaving trials.

Data layering doubles patient recruitment for breast cancer trial

Despite having set up multiple treatment centers, our client was experiencing patient recruitment issues, with levels way below that needed to execute a representative clinical trial. Across 116 sites, only 77 patients had been enrolled in 15 months. These figures are not uncommon in the industry; it is estimated that only 3% of cancer patients participate in clinical trials.[8]

By using the World Health Organization breast cancer prevalence data and overlaying this with Fortrea's patient recruitment and investigator performance data, we were able to locate the most advantageous sites to use in the trial. With access to more than 40% of industry trials being conducted at any one time, our Xcellerate® Informatics suite can give powerful up-to-date, historical performance data. This NH study indicated that 31 nonperforming sites should be closed, and it identified 51 new sites that should be opened, some in new countries that hadn't previously been included in the client's trials. As a result of this new focus on high-performing treatment centers, the client was able to double their recruitment rate, thereby rescuing a failing trial and ensuring its completion.

Embracing more flexible trial designs and providing alternatives to randomized control trials

Randomized clinical trials (RCTs) continue to be the gold standard for testing drugs in patient populations and safely bringing a drug to market. RCTs are highly selective and tightly controlled, measured against a control arm, such as a placebo or, more commonly as more and more diseases have existing treatments, against the current standard of care (SOC). Although RCTs provide a robust method of evaluating the safety and efficacy of new treatments, and most clinical guidelines are derived in this way,[9] they are not always feasible. When drugs are developed for rare diseases, population sizes can be too small to use an active control arm and, in many cases (such as in heavily pretreated patients with advanced cancer), an SOC doesn't exist. Using a placebo also poses ethical issues, particularly where diseases are significantly life-limiting or advanced.

Outside of rare diseases, the use of RCTs can also pose significant issues in trial recruitment and retention. Patients may be more reluctant to be involved in a trial if there is a chance that they will receive a placebo, even though they will receive an enhanced level of monitoring, screening and support throughout the process. Where SOC is used as the control arm, unforeseen issues may also arise, such as the current treatment method changing during the trial period. These adjustments can make it hard to draw valid conclusions about the effectiveness of the intervention when compared against a shifting treatment plan with increasing variables.

As an alternative to placebos or active control arms, NH studies can make use of external data to create a synthetic control arm. Robust external data can be taken from clinically relevant sources, meeting the guidelines set by the FDA,[1] EMA[2] or PMDA[3] and adjusted using statistical methods to create a synthetic control arm. This allows direct comparison of the trial data against pre-existing evidence for a placebo or SOC. The FDA has given assurance that synthetic control arms can be submitted as evidence in regulatory submissions, as long as the external control group is similar to the testing group in all aspects that might affect the outcomes of a trial and that valid epidemiology approaches are taken to reduce selection bias.[1]

In 2020, the FDA approved the first synthetic control arm for a Phase III trial to test a new treatment for a particularly aggressive form of brain tumor: recurrent glioblastoma. The trial uses synthetic control data, derived from NH studies on more than 22,000 previous trials, and combines this with data collected from randomized patients to create a hybrid external control arm.[10] By using this method, the number of patients allocated to the placebo is dramatically reduced, ensuring more patients have access to a potential lifesaving drug while allowing for faster trials that can reduce the time taken to take the drug to market.

The real-world evidence generated by NH studies can help power complex, adaptive trials, particularly those using Bayesian techniques and requiring multiple simulations. With statistically complex adaptive designs, patients can benefit from prespecified in-trial changes; trials can be stopped if adverse effects are observed or drugs redirected if sufficient benefits aren't seen in particular groups.

Borrowing breast cancer knowledge to treat gastric cancer

NH studies are already being used to support innovative trial designs. By drawing on the vast and varied clinical and trial evidence already in existence, statistical methods can be used to draw insights and make connections among studies that tackle different indications. The monoclonal antibody trastuzumab was initially developed to treat breast cancer; it shows efficacy in HER2-positive cancers and has been used as a standard treatment for many years in the U.S. and Europe. NH studies showed that HER2 was also overexpressed in 22% of gastric cancer patients, and with subsequent trials, trastuzumab was shown to reduce the risk of death by up to 26% and extend survival rates by three months. Trastuzumab is now recommended as a treatment option in combination with chemotherapy for patients with advanced HER2-positive gastric cancer.[11]

Trastuzumab's success in multiple HER2-positive indications has seen newer agents follow a similar path. The new antibody-drug conjugate trastuzumab deruxtecan is approved for the treatment of advanced breast cancer and is now being trialed for gastric cancer.[12,13]

Using existing drugs in novel ways and combining therapies to attack diseases from multiple vantage points further increases the suite of therapies available to tackle some of the most serious and life-limiting conditions. These connections can often be unearthed through NH studies.

Developing relationships for accelerated trials

Along with the clear benefits offered by flexible, adaptive and patient-centric trials, NH studies also help foster the relationships needed to accelerate clinical trials. Creating patient-centric trials already moves drug developers closer to the patient, creating a strong relationship and a trial format that is designed to maximize trial and individual success. By recruiting the right patients to the right trial at the right time, recruitment and retention rates increase and trials are completed faster.

This relationship is cemented in the interactions between the patient and the testing center. By researching and connecting with high-quality testing centers and nurturing interactions with the physicians that conduct the trials, developers can ensure that patients are identified earlier and that trials can start and finish faster. In Phase III and IV trials, where large numbers of participants are needed, high-quality testing centers and good relationships are critical to a trial's success.

Beyond the trials and into submission, NH studies can help smooth the journey to regulatory approval. By generating a clinical development plan with confirmed assumptions about epidemiology, regulators can be actively engaged at an early stage with a clear picture of the trial's aims and success criteria. Any potential clinical concerns or approval issues can be addressed early in the study while toxicology studies are completed, thereby accelerating trial deployment and enhancing the chances of its success.

By creating a detailed profile of the disease and its burden within the population, including molecular and genomic data, drug developers can assess the market size and access considerations. Genomic or phenotype drivers can be evaluated, and accurate hypotheses can be made around patient responses or disease burden within subtypes. This information can help target trials to specific regions and indications or be used by payers to produce eligibility criteria and ensure the best responses per investment. By providing these essential real-world studies and engaging payers early in the drug development process, trusted relationships can be created with payers and the clinicians that will eventually triage care and choose treatments.

Using real-world data to drive more accurate trials

As well as expediting trials, NH studies can help to improve accuracy. Since efficacy and effectiveness don't always translate well from clinical trials to the real world, NH studies can help fill that gap, providing important evidence from similar trials that predict how drugs might perform outside of the carefully controlled environment of the RCT. This real-world evidence can be included at any point in the clinical trial, supplementing and supporting patient and practitioner-generated data. Prospective and retrospective studies both have a role to play here and can be used to draw meaningful conclusions about biomarkers, genetics and disease subtypes that might alter how a treatment will perform. Diagnostics and prognostics can work together to inform the course of a trial and the patients' responses to an individual drug. By accessing real-world evidence of a disease, developers can create robust clinical development plans that demonstrate confirmed epidemiological assumptions and clear success criteria—essential ingredients for expedited regulatory submission and improved approval rates.

Patient-centric trials, informed by the real world, deliver more successful outcomes

Thanks to the recent guidance issued by regulatory bodies, NH studies are now considered as important components for every clinical trial phase, from initial market evaluation to Phase IV trials and in-market data collection. And this interest goes way beyond the creation of synthetic control arms for drug trials for rare diseases.

Pharmaceutical and biopharmaceutical organizations can now build a complete picture of a disease and its progression without intervention, helping to:

- Develop a clear understanding of the current standard of care and potential gaps
- Identify potential patients faster and develop relationships with test centers to improve trial recruitment and retention
- Create more flexible and adaptive, patient-centric trials and enable single-arm trials to maximize treatment access, particularly for rare diseases
- Involve regulators, key opinion leaders and other important stakeholders earlier in the trial process through an understanding of the assumptions and aims of the trial
- Provide the level of detail needed for clinicians to triage care and payers to set criteria to signpost patients who are most likely to benefit from the treatment
- Streamline the whole clinical trial process—creating the understanding needed to accelerate trials and provide more successful outcomes

By accessing the wealth of evidence available, NH studies provide the means for drug developers to learn from the successes or failures of trials that have gone before, supported by the epidemiological profile of a disease and its current SOC. This real-world evidence and study-specific data can help developers design faster, more accurate and more cost-effective trials that keep the patient at the center.

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