Duke | MARGOLIS CENTER for Health Policy

Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More

Meeting Summary

Background

The drug and biologic development process follow an established, stepwise approach where the performance of a candidate therapeutic in the clinical investigation phase is critical to receiving regulatory approval through either the accelerated or traditional approval pathway. However, the clinical investigation phase can be long and resource intensive. As the biological mechanisms of diseases and pharmacological activities of drugs are better understood, this information provides opportunities to improve clinical trial efficiency through the use of translational[1] science studies. However, the extent of translational work done within specific development programs varies related to sponsor resources, expertise, availability of translational tools (e.g., animal models, pharmacodynamic biomarkers) and other such constraints. Limited translational efforts may lead to subsequent challenges such as availability of biomarkers that can facilitate development including surrogate endpoints, as well as limitations in additional supportive information regarding drug response that could potentially serve as confirmatory evidence in a subsequent regulatory filing. To explore the role of translational science evidence to support drug development and to identify opportunities and challenges therein, the U.S. Food and Drug Administration (FDA), in collaboration with the Duke-Margolis Center for Health Policy hosted a public workshop entitled, "Translational Science Studies in Drug Development: Surrogate Endpoints, Biomarkers, and More" on May 24th and 25th, 2022. In this workshop, presentations described use cases[2] throughout the drug development process and across a variety of disease areas where translational science studies yielded successful results, as well as situations where efforts were not successful. Subsequent panel discussions highlighted the key themes of collaboration, data standardization, and data sharing that facilitate the use of translational science studies in the drug development process.

Types of Translational Science Studies

Identification of Novel Biomarkers

Discussion in multiple sessions centered on the identification and development of novel biomarkers as candidate surrogate endpoints that could be used in clinical drug development programs. In one case study, a strong understanding of the underlying biology of organic acidemias, rare metabolic disorders, and the ability to move findings between the bench and bedside helped identify new candidate biomarkers. These biomarkers have shown encouraging and significant clinical results. In another case study, a biomarker for cerebral hemorrhaging using non-heme iron mineralization in the brain was identified through quantitative susceptibility maps. Other presentations highlighted the successful translation of biomarkers from discovery to use in regulatory decision-making. One example described

[1] The National Center for Advancing Translational Sciences (NCATS) defines translation as the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public – from diagnostics and therapeutics to medical procedures and behavioral changes. Please see: https://ncats.nih.gov/translation/spectrum

[2] To see the use case presentations, please visit: https://healthpolicy.duke.edu/projects/translational-science-drug-development-surrogate-endpoints-biomarkers-and-more-use-case

how meta-analyses of observational studies, meta-analyses of clinical trials, and simulations of trial design were used to validate the two-slope model of glomerular filtration rate (GFR) decline as a surrogate endpoint for progression to kidney failure in trials of chronic kidney disease. In another, meta-analysis methods were used to assess the suitability of pathological complete response and minimum residual disease as biomarkers in various forms of cancer. These examples highlight the importance of both bench science and clinical research in identifying candidate biomarkers for future use in drug development programs.

Validation of Novel Surrogate Endpoints

Throughout the workshop, discussion touched on the process of validating a novel surrogate endpoint for accelerated approval and traditional approval pathways. FDA described the process for the qualification and development of a biomarker as a surrogate endpoint in available resources[3]. Surrogate endpoints can be characterized by the level of clinical validation as candidate surrogate endpoints, reasonably likely surrogate endpoints, and validated surrogate endpoints. A validated surrogate means that the endpoint is expected to predict clinical benefit. For a biomarker to be considered as a validated surrogate, extensive and robust supporting information, typically from multiple different sources, is needed. A surrogate endpoint that is assessed as "reasonably likely" to predict clinical benefit can support accelerated approval. The evidence needed to support this determination is less than required for full validation, but still is typically strong and from different sources of information. In some cases, meta-analytical methods using data from multiple trials can be useful to establish a correlation between a surrogate and a clinical endpoint, recognizing the limitations of correlation alone as sufficient to support a biomarker as a surrogate endpoint. For example, one case study used data from multiple trials to assess the suitability of pathological complete response and minimum residual disease as biomarkers in oncology. For this process to be effective, many trials must collect the same measurements, and participants noted that stable funding sources help facilitate consistency. Furthermore, in many disease areas, there are multiple biomarkers with the potential to be useful endpoints, participants noted the importance of thinking about what the most appropriate endpoint is, which might vary depending on study phase, population, treatment, and design.

Bridging Biomarkers

Response biomarkers can be used for bridging the efficacy of an intervention via extrapolation from a "source" population to a "target" population, for example, from an adult population to a pediatric population. These biomarkers can be helpful for pediatric extrapolation studies especially when traditional clinical trials may not be feasible due to ethical and logistical challenges. Establishing a biomarker that is suitable for bridging efficacy should satisfy the five core criteria. First, the disease should be biologically similar in children and adults. Second, in adults, the intervention should be safe and effective and have an effect on both the clinical outcome and the proposed biomarker. Third, the biomarker should capture the principal causal pathway through which the disease affects traditional clinical measurements. Fourth, the biomarker should reflect drug responses, operating through other pathways, that may attenuate the drug's clinical effectiveness. Lastly, the clinical effect in the target population should be somewhat proportional to biomarker effects[4]. One use case demonstrated the successful use of pulmonary vascular resistance as a bridging biomarker for the approval of the first drug for pulmonary arterial hypertension in pediatric populations.

[3] https://www.fda.gov/media/115120/download
[4] https://link.springer.com/article/10.1007/s43441-022-00445-6#Tab2

Use of Animal Models

Many translational science studies discussed during the workshop incorporated animal models as key components of their investigative frameworks. Use cases of note included the presentations on Hutchinson-Gilford progeria syndrome and organic acidemias. Animal models can generate important preclinical data and can be especially helpful in rare diseases where the small number of patients may limit the number of clinical studies or trial designs that are typically conducted for prevalent diseases. These models can also help establish proof of concept for a treatment, such as the transgenic mouse model that helped establish evidence of effectiveness for the progeria treatment, lonafarnib. However, there can be limitations to using animal models for preclinical research, including that animal models often have low throughput, and the disease being modeled may present different pathology in animals versus humans, which can limit the usefulness for drug development.

New Approach Methodologies

The final translational science studies discussed involved New Approach Methodologies (NAMs), which are broadly defined as approaches to toxicology testing that do not involve animal testing, for example, the use of stem cells, engineered tissues, or mathematical modeling[5]. NAMs have the potential to reduce the cost and increase the speed of toxicity testing and dose selection, improving the drug development process. In one presentation, a model using human primary cells was successfully used to define a therapeutic index, minimize risk, and improve starting dose selection in a T-cell bispecific antibody therapy in Wilms' Tumor 1 in Acute Myeloid Leukemia. In vitro techniques like these can help minimize risk to patients by providing information on toxicity prior to testing in humans.

Challenges During Development and Validation

Throughout the meeting, presenters and participants explored the challenges associated with the development and validation of candidate biomarkers and surrogate endpoints for use in translational science studies. One challenge highlighted was that candidate biomarkers in any disease area need to be robust enough for potential use as surrogate endpoints in studies. Failure to achieve validation as a surrogate endpoint could happen for many reasons, including the inability to link the candidate to a clinically meaningful outcome, inability to establish biological mechanism/relevance, and lack of responsiveness to treatment. Furthermore, the biomarker may only correlate to a clinical endpoint in a very limited subset of patients, so it is not generalizable to the intended population. Examples of this include a mismatch in biomarker response between acute and chronic stages of a disease or a mismatch between individual level and population level data.

Rare diseases of all types present similar challenges during biomarker and surrogate endpoint development due to the small population size. As a result, generating sufficient data can be extremely difficult. To address this, some patient advocacy groups and centers of excellence have created registries to capture as much data as possible on patients for use in the future. Historical data allows researchers to supplement small population sizes. However, historical data may not always capture the necessary samples or measurements needed to establish baselines or assist with validation processes. Furthermore, researchers may need to re-obtain written informed consent for subsequent studies using historical data, which, while not impossible, can present significant barriers.

[5] https://www.fda.gov/media/144891/download

Particular disease areas may also face niche challenges in the development space. Presenters from the neurodegenerative disease space highlighted difficulties in biomarker development and validation. Currently, a major hurdle for many neurodegenerative diseases is the inability to validate candidate surrogate endpoints because available treatments lack an effect on clinically meaningful endpoints. In Alzheimer's Disease (AD) specifically, β-amyloid biomarkers can be measured in either blood or cerebrospinal fluid. Measurement in blood is more desirable due to ease of access and overall patient comfort, but the presence of circulating β-amyloid made the identification of a suitable biomarker uniquely challenging. While diagnostic enrichment biomarkers are not currently suitable for use at the individual level, there has been progress in the development of these biomarkers for AD.

Best Practices for Driving the Use of Translational Science Studies

Collaboration

Participants in multiple sessions emphasized the importance of collaboration to successfully use translational science studies in drug development programs. Participants acknowledged that the inclusion of all stakeholders, such as basic science researchers, clinicians, patients, and regulators in discussions is critical to the utilization of these studies. Open, ongoing dialogue between these groups was acknowledged as a mechanism to improve collaboration, rather than one-off meetings on the topic. Additionally, collaboration is critical since data to support new biomarkers and surrogate endpoints must be strong and extensive, and data sharing is an important approach to creating a sufficiently robust data set. The power of collaboration was demonstrated by the use case focusing on the development of GFR slope as a surrogate endpoint in chronic kidney disease. Research into surrogate endpoints for chronic kidney disease started as requests from regulators to investigators. As trust was built and the results were reported at the National Kidney Foundation annual meetings, interest in the surrogate endpoints by the community of stakeholders grew. The regularity of updates on this research was acknowledged as keeping stakeholders engaged on the topic and usage of the candidate surrogate endpoints was increased because the information was disseminated into the community. This led to sustained and adequate funding for dedicated research into additional candidate surrogate endpoints, including GFR slope, which could be used in drug development programs.

Collaboration can also further accelerate the adoption of innovative research methods, such as NAMs, and the adaptation of measurement techniques from one disease area to another. For example, a gait test for geriatric patients was modified for use in a pediatric population who were also struggling with mobility due to their rare disease. Open discussion with experts in both disease areas as well as with regulators led to the successful modification and inclusion of this test in the regulatory approval package.

Finally, collaboration across areas of expertise and disease areas was discussed as a strategy to drive innovation and research into biomarkers and surrogate endpoints. For example, participants noted that large consortia, like the Critical Path Institute and Friends of Cancer Research, are particularly well suited to host and facilitate these multidisciplinary discussions. These consortia are already working on topics such as the use of neurofilament light chain in several neurodegenerative diseases and the measurement of circulating tumor DNA in different cancer types. Regulators highlighted that early discussion and engagement can help shape research on candidate biomarkers and surrogate endpoints and considering how to incorporate translational science studies early in the drug development process may increase the chances of obtaining regulatory approval later.

Data Standardization

During discussion, participants brought up the importance of standardization to help drive the development and validation of biomarkers and surrogate endpoints. Standardization can take many forms and can play an important role to address common challenges that arise during translational science development programs. The first form is the standardization of results, which describes the reproducibility of measurements across different assays or different users and laboratories. This reproducibility is critical to the qualification of a novel biomarker and obtaining regulatory acceptance for these biomarkers. It is important to consider this early in the design process, and stakeholder collaboration to prospectively identify common methods for measuring the candidate biomarker can help achieve a robust set of results.

The second form of data standardization is alignment on common variables and data points across research studies and across disease areas. Collecting a set of core or common data points, including potential biomarker candidates, makes the aggregation of data from related trials easier and allows for a more streamlined meta-analysis. Collaboration between multiple research organizations to align on common, prospectively defined methods is critical to moving towards regulatory acceptability in the most efficient manner possible. Participants discussed examples in which biomarker validation efforts were hampered because the disease-relevant clinical trials did not integrate biomarkers and lacked standardization, which made data aggregation later extremely difficult and posed significant challenges. A concerted effort to consider standard variable and data point inclusion at the outset of trial design was acknowledged as a way to address these challenges.

Again, participants identified that large consortia are well positioned and uniquely suited for convening stakeholders to discuss, identify, and agree to a set of common data points for usage. Additionally, they can help direct research and validation efforts of biomarkers and surrogate endpoints across related disease areas to the benefit of all.

Data Sharing

Participants identified improved data sharing, particularly when clinical outcomes are known, as a mechanism to facilitate the use and inclusion of translational science studies in drug development. Participants acknowledged that industry stakeholders may be reluctant to share proprietary data, so expanding data sharing infrastructure in a pre-competitive space is critical. Building trust among all stakeholders is key to success, so that those stakeholders, particularly industry partners, are willing to share information.

Participants stressed that access to shared data is critical for the identification and development of biomarkers and surrogate endpoints, particularly for multivariate models of disease. For example, researchers used machine learning to derive a 27-protein prognostic model for cardiovascular disease using plasma samples and clinical outcomes collected from over 30,000 clinical trial participants. The development and validation of this model relied on the aggregation of large datasets representing heterogeneous patient populations. Though variation in patient populations is generally seen as a limitation in traditional clinical trials, variation within training data allowed for better machine learning and corrections during the development of this model.

It was also noted that the implementation of the General Data Protection Regulation[6] has been a significant hurdle to data sharing internationally and the implementation of data sharing agreements can be a long and laborious process. Participants further noted that the critical importance of data sharing pushes stakeholders to engage in this process of negotiating data sharing agreements. Once again, participants pointed to large consortia as being well positioned to bring together all parties as well as house large data sets.

De-Risking Translational Science Studies

Several participants noted that the incorporation of translational science studies can be risky for sponsors. Minimizing those risks is the result of the successful implementation of the three themes: collaboration, data standardization, and data sharing. Participants continued to identify consortia as being well-positioned to convene multiple stakeholders as well as house and manage large, accessible data sets. Working in collaboration with other stakeholders and identifying the risks for each group can allow the entire group of stakeholders to collectively identify methods to de-risk research, which is critical for the development and incorporation of translational science studies into drug development programs and improve the process more broadly.

[6] https://gdpr-info.eu/

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