Coming Out of the Dark: A Wholistic Approach to Therapeutic Development

Summary Report from *DIA 2023 Global Annual Meeting* Solution Room

Introduction

The development of efficient solutions for patients is impeded by a multitude of challenges that require collective efforts from researchers, policymakers, and other stakeholders. By addressing issues such as drug repurposing, biomarker validation, patient involvement, and regulatory clarity, the healthcare industry can pave the way for more effective treatments and improved patient care. These obstacles have proven to be significant roadblocks, impeding progress towards innovative treatments and therapies, with life-altering implications for patients.

Collaborative endeavors and innovative strategies will be crucial in overcoming these challenges and making meaningful advancements in medical science.

During the *DIA 2023 Global Annual Meeting* in Boston, a multistakeholder group participated in a solution room to discuss and explore what is needed to prepare for the future state of therapeutics development. Participants in the workshop:

- Discussed and summarized the challenges and benefits of each therapeutic class.
- Prioritized which challenges are most impactful for decision making in therapeutic development.
- Brainstormed potential mechanisms to overcome barriers.

Peter Sorger and Mark Albers chaired the workshop. Dr. Sorger is the head of therapeutic science at Harvard Medical School, and Mark Albers is an assistant professor of neurology at Harvard Medical School and the Frank Wilkens Jr and Family Endowed Scholar in the Department of Neurology at Massachusetts General Hospital.

DIAmond Session

A DIAmond session titled “A Case Study for Illumined Therapeutic Development: Shining the Light on ALS” moderated by Peter Sorger set the stage for deeper roundtable discussions in the solution room through discussion of the hurdles that still exist in the development of therapies for ALS. Participants on the panel were Mark Albers; Nazem Atassi (head of Early NeuroDevelopment, Sanofi); James Berry (assistant professor of neurology, Massachusetts General Hospital; co-director of the MGH Neuromuscular Division and ALS Unit, Massachusetts General Hospital); Steven Kowalski (Patient Advocate, ALS, United States); Lahar Mehta (head of Global Clinical Development, Amylyx Pharmaceuticals); and Stacy Rudnicki (vice president, Clinical Research and Development, Cytokinetics).

This panel focused on recent advances in the development of effective therapeutic options for amyotrophic lateral sclerosis (ALS), which demonstrate the promise of a range of modalities, progress in the approach to streamlining clinical trials, and the benefits and promise of integrating novel endpoints into research to better describe outcomes. These advancements in the ALS development ecosystem create an opportunity to better integrate patient preference, consider prioritizing the role of survival versus other endpoints in therapeutic development, and provide an opportunity to translate lessons to other therapeutic areas.

Roundtable Discussions

Following the DIAmond session, participants were split among three tables for discussion. The tables were led by Peter Sorger, Mark Albers, and Karla Childers, senior director of strategic projects in the Johnson & Johnson Office of the Chief Medical Officer. Each table discussed the following questions (summaries of the discussion points are detailed below each question):

What are the primary challenges hampering the efficient development of solutions for patients? If we could solve three of these challenges today, which should be prioritized?

Reluctance to Repurpose New Drugs

One prominent challenge is the reluctance to repurpose new drugs. While existing drugs may hold promise for new therapeutic indications, there exists a hesitancy to explore such possibilities, which could potentially provide faster routes to clinical application. This reluctance stems from the risk-averse nature of the pharmaceutical industry, as well as regulatory hurdles surrounding drug repurposing. By addressing this issue, researchers could unlock untapped potential for treating patients more effectively.

Lack of Validated Biomarkers

Another critical concern is the lack of validated biomarkers. These biomarkers are essential for patient selection, stratification, and assessing target engagement, significantly impacting treatment development. The absence of reliable biomarkers hampers the identification of suitable patients for clinical trials and slows down the process of bringing novel therapies to market.

To overcome these challenges, fostering precompetitive collaboration and funding for biomarkers is essential. By promoting collaboration among researchers and companies, valuable insights can be shared, and progress can be accelerated. Establishing the best biomarkers for various diseases is a collective effort that requires extensive research and collaboration.

Variability in Disease Progression

Moreover, variability in clinical care and disease progression adds complexity to patient treatment. Understanding the sources of this variability, particularly between slow and rapid disease progression, is crucial to providing personalized care and developing tailored therapies. By delving into the biological basis of this heterogeneity, researchers can develop more effective treatment strategies.

Regulatory Inconsistencies and Reimbursement

A persistent issue in the healthcare industry is the need for clarity on regulatory inconsistencies that affect reimbursement. The lack of uniformity in reimbursement policies creates uncertainty for companies, hindering their investment in innovative therapeutic approaches. Clear and consistent regulatory guidelines are essential to incentivize pharmaceutical companies to pursue drug repurposing efforts and invest in research and development.

Reimbursement and pharmaceutical incentives are intertwined challenges. To improve access to treatments, it is essential to address pricing and reimbursement issues. Creating a more supportive environment for pharmaceutical companies, while ensuring fair pricing and availability, would enhance treatment possibilities for patients.

Patient Participation in Clinical Research

Patient involvement in research and clinical care is a critical aspect that needs to be addressed. Empowering patients to influence the importance of biomarkers and endpoints would ensure that treatments align with their specific needs and experiences, improving overall patient outcomes.

Additionally, the lack of large sample sizes and controlled clinical trials makes it challenging to obtain robust and reliable data for evaluating the efficacy of potential treatments. By increasing patient participation in clinical trials and employing more rigorous study designs, researchers can gather more comprehensive evidence for novel therapies.

ALS presents specific challenges due to the limited participation of patients in clinical trials and the heterogeneity of disease progression among patients. Encouraging ALS patients to engage in clinical trials and establishing rare disease consortiums can promote collaborative efforts and accelerate research progress. Investing in early patient involvement and education can further facilitate these efforts.

How might we overcome the identified challenges or gaps? What steps can we take now and in the future?

Biomarkers and Endpoints

Focusing on biomarkers reflecting the disease pathology and developing novel digital endpoints can lead to more sensitive and objective measures of treatment efficacy. Including patient input in endpoint development ensures that treatments align with patients' needs and experiences. Incorporating exploratory biomarkers in clinical trials and publicly sharing data can enhance patient selection, stratification, and treatment response assessment. This can lead to more targeted and effective therapies, accelerating the drug development process.

Translation and Validation

Innovative trial designs and agreement on how to handle missing data from animal models can improve the translation of preclinical findings to human trials, reducing drug development timelines and enhancing success rates. Moreover, translating and validating survey endpoints and introducing new and improved human cell models can provide more robust and relevant data for clinical decision-making.

Heterogeneity of Disease Progression and Patient Experience

Developing quantitative disease progression models and identifying sources of treatment response variability can lead to more accurate staging of the disease, facilitating the design of tailored treatment strategies for individual patients. To aid this approach, sharing existing data, validating surrogate endpoints, and conducting natural history studies can help us better understand and manage disease heterogeneity, leading to more successful clinical trials. Leveraging tissue chip models, biomarkers, real-world data, and AI can further help manage disease heterogeneity, leading to more personalized treatment approaches that consider the unique characteristics of individual patients.

Harmonization among Health Authorities

Achieving harmonization in the acceptance of the ALS Functional Rating Scale-Revised (ALSFRSR) by health authorities can streamline the regulatory process, ensuring that patients in multiple regions get faster access to treatments. Additionally, streamlining the clinical trial process through the ACT-EU initiative can expedite the development and approval of ALS treatments, providing patients with faster access to potential therapies.

Improving Patient Recruitment Methods and Leveraging Technology

Enhancing patient recruitment methods and leveraging technology advancements can increase patient participation in clinical trials, ensuring that trials are adequately powered and representative of the patient population.

What impact could these opportunities have on the development and prioritization of treatment modalities?

Overall, embracing these opportunities in treatment development can lead to more efficient and successful clinical trials, harmonized regulatory processes, personalized treatment strategies, and increased interest from pharmaceutical companies in developing ALS therapies. These actions have the potential to bring much-needed advancements in ALS research and improve patient outcomes.

Who are the people who need to be involved to harness opportunities?

Harnessing these opportunities requires collaboration among various stakeholders, including Institutional Review Boards (IRBs), Ethics Committees (ECs), regulatory agencies like EMA and FDA, research centers, and other relevant organizations.

What are the considerations in the use of survival versus a surrogate endpoint for efficacy decision making?

Survival endpoints are thought of as clinically meaningful as they directly measure the ultimate goal of treatment, which is to prolong the patient's life. They provide a clear and objective measure of treatment efficacy, especially in diseases with a well-defined and predictable progression. However, their use can be limited by the time required to observe meaningful differences in patient outcomes, which can prolong clinical trials and delay drug approval. What's more, patient preferences, such as quality of life (QoL) and symptom relief, may not be fully captured by survival endpoints, leading to potential discrepancies between treatment benefits and patient needs.

In contrast, surrogate endpoints, like QoL and ALSFRSR, can offer more accessible and shorter-term measures of treatment efficacy, allowing for faster decision-making in clinical trials. They may also provide insight into the patient's experience, capturing aspects of the disease beyond survival. One of their disadvantages includes the need to thoroughly assess their validity to ensure that the chosen surrogate endpoints reliably reflect treatment effects on the ultimate clinical outcomes. Additionally, the use of surrogate endpoints can be particularly challenging in diseases like ALS, where disease progression and patient status may introduce variability in treatment responses.

Does this differ by disease or by progression of disease/patient status?

Disease and patient status can influence the choice of endpoints used in ALS research. For example:

- In the early stages of the disease, functional endpoints like ALSFRSR may be more relevant, while survival endpoints might be more appropriate in later stages.
- The use of functional endpoints as primary measures can provide valuable information about treatment effects on patient functionality and quality of life.
- Quantification of outcomes can help standardize the assessment of treatment effects across different patient populations.
- Assessing QoL and Patient-Reported Outcomes (PROs) can offer insights into the patient experience and satisfaction with treatment.

In conclusion, the choice between survival and surrogate endpoints in ALS research involves considering the trade-offs between the clinical significance of survival and the accessibility and practicality of surrogate measures. Disease and

patient status also play a crucial role in determining which endpoints are most relevant and informative. A comprehensive and thoughtful approach is necessary to strike a balance between these considerations and make informed decisions for effective treatment development in ALS.

What is the role of patient preference?

Patient preferences hold significant importance in the treatment of ALS. Since survival outcomes in ALS can vary greatly, understanding and respecting patient choices is essential in managing the disease and determining treatment approaches. Patients' individual preferences can influence the decisions they make regarding their care, including treatment options and end-of-life decisions.

Assessing patient preferences is also critical for evaluating the quality of care provided and determining the value of different endpoints in clinical trials and research. By considering patient preferences, healthcare providers and researchers can tailor treatments and interventions to better meet the needs and desires of individual patients.

Collecting more patient data on preferences is key to making informed and patient-centered decisions. This data will serve as a foundation for enhancing decision-making processes in ALS care and research. By incorporating patient perspectives, healthcare professionals can improve the overall patient experience and optimize treatment strategies that align with patients' values and goals.

What is needed to integrate this thinking?

To successfully integrate the above thinking around developing treatment solutions for ALS patients, several steps are necessary. Firstly, collating and analyzing multiple data sets from clinical trials is essential to gain comprehensive insights into patient preferences and treatment outcomes. This data-driven approach will help inform decision-making and improve patient-centered care.

Secondly, reaching an agreement on the requirements for standardized endpoints is crucial. Consistency in measurement and assessment will enable better comparison and evaluation of treatment efficacy, leading to more reliable conclusions.

Furthermore, fostering collaboration among various stakeholders, including pharmaceutical companies, regulatory bodies, and payers, is essential. By working together, these entities can pool resources and knowledge to address specific challenges in ALS treatment and research effectively.

Lastly, developing evidence-based standards for novel endpoints will contribute to the credibility and reliability of research outcomes. These standards will ensure that the chosen endpoints accurately reflect treatment effects and are relevant to patient experiences.

By implementing these measures, the integration of patient preferences, standardized endpoints, and collaborative efforts will lead to more patient-centric ALS treatments, streamlined research processes, and improved overall patient outcomes.

Conclusions

Opportunities exist to collaborate in ways that can create efficiency in finding new treatments for ALS. For example, leveraging existing data sets from organizations like Sanofi, Biogen, Amylyx, and MIT offers a viable strategy to advance innovative therapies and treatment modalities in ALS. Consensus on meaningful evidence-based endpoints can also contribute to more efficient and effective development programs. These efforts will require strong leadership and collaboration among stakeholders to address the challenges and gaps in treatment development effectively. By working together, these efforts aim to enhance patient outcomes and improve accessibility to effective treatments for ALS.

Workshop Participants

Table Discussants: Karla Childers – J&J; Peter Sorger – Harvard Medical School; Mark Albers – Harvard Medical School

Participants: Nazem Atassi – Sanofi; Munish Mehra – TigerMed; Stuart Ince – BVMI Bio Consulting; Sabine Haubenreisser – EMA; Steven Kowalski – Patient Advocate; David Schoenfeld – Mass General Research Institute; Lahar Mehta – Amylyx; Stacey Rudnicki – Cytokinetics; Samantha Rubino – QurAlis; Klaus Romero – C-Path; James Wabby – USC; Taylor Gray – QurAlis; Lisa Tatterson – QurAlis; Ralf Harold – EMA; Teresa Allio – Bayer Pharmaceuticals; James Berry – Harvard Medical School; Ebony Dashiell-Aje – Biomarin; Joni Rutter – NCATS, NIH

DIA Staff Contacts: Dr. Sandra Blumenrath, Managing Editor, DIA Publications, and Dr. Courtney Granville, Global Head of Science and Scientific Strategy