VIEWS AND OPINIONS

PATIENT ADVOCACY PERSPECTIVE

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EMBRACING INNOVATION: A PATIENT ADVOCACY PERSPECTIVE ON EVOLVING TRIAL DESIGNS

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SMA Schweiz and SMA Europe, two patient advocacy organisations for the rare condition spinal muscular atrophy (SMA), work towards promoting the fastest possible access to safe and effective medicines for all individuals who can benefit from them. Their experience has shown that patient and public involvement at the design stage of clinical research directly impacts a product's pathway to patients and leads to a better understanding of a product's value later on. Furthermore, recent discussions about how complex clinical trial designs and decentralised clinical trials use innovative methods to conduct clinical research indicate their potential to make trials more flexible, personalised, and convenient for participants. In addition to helping shift current paradigms, innovative trial designs hold enormous potential to further advance medicines for the good of patient communities, especially in the area of rare diseases.

Science has evolved significantly in recent years, thanks to innovative approaches to biomedicine, engineering, and data science as well as the combination of different research fields. Advances in science and research, however, usually outpace changes to regulatory frameworks, leading to misalignments in innovation and regulation and ultimately delaying patients' access to new treatments. One of the current challenges in research is determining how to integrate innovative approaches into product development so that these advances can create value for society.

COMPLEX TRIAL DESIGNS: ACHIEVING GREATER EFFICIENCY THROUGH FLEXIBILITY

Although the randomised controlled trial (**RCT**) design is standard in clinical research, it may not always be the most appropriate approach to address complex research questions. Complex innovative trial designs integrate novel statistical and methodological techniques to address new, more complex biomedical research questions. These trials designs can be particularly promising when conventional approaches may not be feasible or optimal, such as for rare diseases where population sizes are small or for conditions that cover a wide spectrum of phenotypes, and when outcome measures are complex and not tailored to specific conditions. In these cases, the RCT design is often too rigid with narrow eligibility criteria for homogeneous study populations, results are limited in their capacity to be generalised and to reflect the real world, and the studies often take too long.

Patients need more flexible and efficient ways to assess the safety and efficacy of medical products. Adaptive designs allow changes to be made to the study protocol during the trial based on (preliminary) analyses of collected data. More efficiency can also be obtained by using computer simulations and natural history models, by recruiting more heterogeneous study populations, by using external or historical control data, and by incorporating prior knowledge into the design to supplement or replace placebo arms. These new methods have practical implications and can translate into a reduction in the number of participants needed, greater diversity in inclusion criteria, faster recruitment, accelerated and optimised product development, and more tailored treatment decisions. They may also increase feasibility, particularly for studies of rare and ultra rare conditions whose communities have unmet medical needs. Using a complex innovative trial design may be the only way to develop and deliver a product to these communities, which in turn increases knowledge about rare conditions.

DECENTRALISED CLINICAL TRIALS: INTEGRATING CLINICAL RESEARCH INTO PARTICIPANTS' DAILY LIVES

Traditional clinical trials require participants to invest a significant amount of time, cause inconvenience, and require a high degree of mobility since participants must travel to the trial site for study visits. This can place a burden on participants in terms of managing the logistics of their daily lives and organising travel when living with a disability or an illness. Trial participation also has an impact on participants' work, school, social environment, and family members (e.g. spouses, children, and siblings). The burden of participation and disruptions to participants' daily routines can be minimised in decentralised clinical trials (**DCTs**) because study visits are (partly) transferred from the trial site to participants' homes. DCTs also increase autonomy and convenience. In addition to benefiting participants with rare diseases such as spinal muscular atrophy, DCTs can positively impact participants recruited across borders. Traditionally, SMA Europe has supported cross-border recruitment because cross-border studies are often the only opportunity for individuals with a severe, progressive condition to gain access to a potentially life-saving product. Being selected to participate in such clinical trials is often the last ray of hope for patients with no other treatment options. Therefore, the opportunity to participate in a study outweighs the direct and indirect costs associated with travel. Any tool that can ease this enormous, but sometimes necessary, burden is welcome.

MOBILE TECHNOLOGIES: INCREASING THE RELEVANCE OF OUTCOME ASSESSMENT

Not only is trial design undergoing a transformation, but the way data is collected in clinical trials is becoming more patient-centric – a trend driven by the COVID-19 pandemic. Mobile technologies (e.g. wearables) offer potential value, especially when studying conditions for which outcome measures are complex. In many rare conditions, defining endpoints and measuring them with traditional methods does not adequately capture meaningful outcomes. Mobile technologies provide the opportunity to innovatively collect data during studies, including real-time data and more continuous data in people's living environment. Especially in rare disease communities, the opportunities to bring treatments to a specific community are limited. It is no longer acceptable to run the risk of a therapy being rejected that is effective in itself because researchers have not been able to measure potential, patient-relevant effects using traditional measurement approaches. Collecting data using mobile technologies can be a tool to address this issue. However, this should not be limited to capturing electronic patient-reported outcomes, collecting information on physical function, or gathering spatial information (e.g. movement) – the sky should be the limit.

PATIENT INVOLVEMENT: PURSUING A TRANSDISCIPLINARY APPROACH TO CLINICAL RESEARCH

As mentioned above, it is crucial to minimise the risk of hampering clinical development for rare diseases. This applies not only to systemic frameworks and investments but also to study participants. It is paramount to recruit informed participants who have the capacity to comply with study requirements (e.g. have the language, cognitive, and mental capacity as well as the technological savviness required), even more so in the light of the advances described above. In addition, study teams need to reassure participants about the data security and the safety of using continuous mobile monitoring tools in their private environment. Researchers must also work together with patient organisations – not only to educate and raise patient communities' awareness of these tools and opportunities but also to consider their lived experiences, understand their needs and preferences, and identify what endpoints are most relevant to patients in order to best capture them using all the technological advances available.

INNOVATIVE RESEARCH APPROACHES: MOVING CLINICAL RESEARCH FORWARD

More individualised and precise research approaches are important in clinical research, particularly for rare diseases. They can lead to protocols and data collection that are more convenient and relevant to patients and can promote the inclusion of a larger part of the population, which further improves study recruitment and retention rates and leads to earlier trial completion. Further, they have the potential to generate more data and knowledge on safety and efficacy across the spectrum of a condition and can have a direct, positive impact on the availability of products to patients. The broader application of innovative and adaptive research and the increased use of (mobile) technology-assisted methods can help to bridge today's gaps and move clinical research forward – while making sure no one is left behind.

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