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ESSENTIALS Engagement of patients during the development of new treatments has evolved rapidly in the last decade. No longer should patients be viewed as passive subjects of research: they should be active partici- pants in a more open and ambitious ecosystem of academic investi- gators, companies, and government entities. Enhanced engagement of patients throughout the development process provides important benefits for the introduction of useful and effective drugs by chan- ging the understanding of the disease, the measurement of the dis- ease during treatment, and the interpretation of benefit-risk. This system is critical for the discovery, study, development, regulation, delivery, and use of innovative therapies. Introduction Increasing involvement of patients and their advocacy organizations in therapeutic development provides an opportunity to innovate experimental medicine and render challenging or invasive clinical trials possible. The recent excitement in the field of ‘rare diseases’ has a long history—but since the accelerated introduction of novel treatments as a result of the introduction of the Orphan Drug Act (first in the United States, in 1983, later followed in Europe in 2001), participation of patients in the whole process of therapeutic devel- opment has burgeoned at many levels. There can be little doubt that this trend of practice substantially improves the development of drugs and promotes a healthy social contract between all parties that can accelerate achievement of one common goal: introduction of ef- fective and safe treatments. For academic investigators, clinicians, companies, and government entities, the goal is common; but the processes undertaken by, and investment of each party is strikingly different. As to the involvement of patient organizations, this may include funding creative breakthrough research at a university that might otherwise not be able to provide adequate support for the neces- sary preclinical or clinical studies. Patient groups have contributed materially to the development of new ways to measure or score the manifestations of a given disease, as well as its response to potential treatments—not least by helping to recruit patients for exploratory clinical research. More recently, patient groups have also

partici- pated in the collection of data on the benefits and risks for treatments relative to their disease, as perceived by the individual experien- cing that condition (the ‘patient perspective’). Finally, many patient groups assist regulatory authorities, such as the European Medicinal Agency (EMA), directly and extensively. This involvement relates to policy changes that are needed to allow early access to therapy or other policies that have significance for patients. Input from patient organizations has broadened the perspective of the regulatory agen- cies as they evaluate new treatments for approval: this involvement is relatively new but provides insights beyond those offered by pro- fessionals in academia and industry—moreover it helps to maintain the focus of the approval process on those most critically affected by a given condition. Enhanced engagement of patients throughout the development process provides important benefits for the development of useful and effective drugs by changing the understanding of the disease; the measurement of the disease during treatment, and the interpret- ation of benefit-risk. The understanding of disease is deepened as a result of detailed disease surveys or studies into the natural course of the condition in the absence of specific treatment, the course of the condition treated or in the context of standard care; here again such work is often supported or organized by patient groups. By these means, those who develop drugs, as well as investigative phys- icians gain a sharper and more quantitative understanding of the true burden of illness in a given disease. It is surprising how often these more intensive and systematic studies cast aside historical in- accuracies and mistaken assumptions created decades before as a result of received clinical wisdom. In the era before treatments were introduced, much knowledge was based on available authorities who had, in reality either seen only one subset of a disease and were unaware of its true diversity: lacking the ability to advance clinical care, little experience of the condition gained through long-term clinical monitoring and follow-up. To study how a treatment affects a disease, studying the disease at a deep and quantitative level is critical for determining how ex- perimental therapies can have an impact on the clinical course. Such detailed knowledge allows investigators to devise more ef- fective instruments of measurement, and at times radically different 2.9 Engaging patients in therapeutic development Emil Kakkis and Max Bronstein

 evaluations and determinants of the progression of a disease, by which treatments can be assessed authentically. Many patients now participate in ‘no-drug’ studies: here, testing methodologies are studied carefully to develop the best measures by which cap- ture the particularities of a given disease. Lately, one of the more compelling effects of patient engagement has been revealed in the assessment of benefit and risk of treatments. For some devastating disorders, the patient and their family’s view of relative risk and benefit can be starkly different from that of physicians or regulators. The quantitative collective of the risks for a disease relative to the additional effects of treatment, allows investigators and regulators to scrutinize the merits of a treatment while accounting for the risks in a devastating disease at the same time. Orphan medicinal products In recent years, the development of therapies for rare or ultra-rare diseases, often referred to as ‘orphan drugs’ or medicines is receiving increasing attention. This is a welcome sea change for patients and their respective advocacy organizations, although it is estimated of the 7000 rare diseases, only 5% have marketed therapies available to patients. There are a wide variety of challenges and opportunities that are unique to rare disease therapy development, but economics may be the most pronounced stumbling block. That is, financing the testing and successful development for a small patient population may be difficult to statistically demonstrate (as a consequence of small sample size) and cost prohibitive for investors and others who seek to earn a return on investment.

Nonetheless, breakthroughs in genetic testing, gene therapy, enzyme replacement therapy have al- ready demonstrated substantial clinical benefit and potential for pa- tients who previously had little hope of access to effective medicines. While the science around rare diseases has progressed rapidly, in some cases, it has outpaced the ability of regulatory agencies to effectively monitor these developments and account for them in ap- proval decisions. In general, both the Food and Drug Administra tion (FDA) and EMA are largely on par for approval of orphan therapies (see Fig. 2.9.1), but the EMA is seen as often providing additional flexibility on the types of data packages submitted to sup- port approval and marketing of an innovative therapy. For example, several orphan therapies have been approved earlier for marketing in Europe, but have been declined or delayed in the United States usually because of issues surrounding the phase 3 studies. In com- plex settings, the EMA has relied on their scientific and medical in- sights into the total package of data to allow a patient population with high unmet medical need access to the drug whereas in the United States, a missed primary endpoint in a phase 3 study has gen- erally not been approved. The contemporary clinical development process While in the minds of many scientists and most employees in com- panies, the clinical trial is the principal focus of their endeavour, the truth remains that clinical trials are indeed another form of experi- ment, with effectiveness and safety still incompletely understood in broader human populations. All the clinical phases of trial pro- grammes are part of a sequence that is in effect an uncertain journey to the ultimate set of goals involving regulatory approval of a safe and effective therapy; and one that is both useful and reimbursed. Before this stage is even contemplated, even the road to initiating an early clinical trial can be long, arduous, and very costly. Identifying a suitable drug target can take years of research and development, with a notably high failure rate. Most early research ideas never make it to clinical trials, and those that do, still have a small possi- bility of reaching an approval. The regulatory process is designed to test safety and efficacy into various stages, and over time these tests do help provide some basic level confidence that a drug is safe and 50 45 40 35 30 25 20 15 10 5 0 2010 2011 2012 2013 Year Approval of new molecular entities (NMEs) 2010–2015 Number of NME approvals 2014 2015 Orphan EMA approvals Orphan FDA approvals All EMA approvals All FDA approvals Fig. 2.9.1 Approval of new molecular entities.

120 section 2 Background to medicine works. No doubt also, however rigorous the regulatory system, it can also fail by approving a drug for a population for which the risks were not well defined, or by failing to approve a drug that might ac- tually benefit some patients, but not those originally studied. Nonetheless, once a suitable small molecule or biological drug candidate has been identified, typically employing in vitro and/or in vivo models of disease, then extensive pharmacological studies, including toxicology are undertaken. This is to verify the reasonable likelihood of safety of the compound before the clinical trial pro- gramme can be planned in any detail. Once completed, and submitted for scrutiny to regulatory au- thorities, then the clinical trial process can move forward in that country for which regulatory approval for clinical trials has oc- curred. In recent years, patient groups have become well-organized and highly engaged with the early research process: some, directly fund preclinical research projects through grant programmes or other charitable mechanisms. In the intense world of rare diseases, families of patients have been known to go so far as to form their own biotechnology company in order to recruit the funding re- quired to treat their family member (see, for example, The Cure by Geeta Anand). Clinical trials are typically divided into several phases—each encompassing a growing cohort of patients. At each stage, there are rich opportunities for patients and their organizations to engage. Phase 1 of clinical development This phase marks the first opportunity for a novel therapy to be

administered to patients. The primary objective at this stage is to determine the safety profile of the compound. During phase 1 clin- ical research, to determine how dosing impacts the safety profile, varying doses of the compound or biological agent are administered to small cohorts of patients. Throughout this process, patients are closely monitored for adverse events and researchers will observe how the compound is metabolized in the body. In addition, some clinical trials may also experiment with different routes of admin- istration for the compound (i.e. oral, infusion, sublingual, and so on). It is important to note that if the phase 1 study reveals high or unacceptable toxicity in patients, the trial may be halted and future development may be completely scrapped. Phase 2 of clinical development Once a safety profile has been established using clinical data, the trial can proceed to the next stage in order to explore the clinical effectiveness of the therapy —'efficacy'. During this period, clinical researchers are obliged to select various endpoints or health metrics that will unambiguously determine the potential benefit of the pu- tative treatment on patients for whom the licensed product is envis- aged. Clearly the selection of what regulatory authorities will agree to as informative clinical trial endpoints vary widely and depend entirely on the disease in question. Some more traditional measures are: overall survival time, severity of symptoms, and quality of life. Alternatively, if known, clinical researchers may attempt to use a biomarker or other alternative measure, which is often referred to as a surrogate endpoint. In some quarters, surrogate endpoints are becoming increasingly favoured by those who develop innovative medicines; this is because they can provide more precise measures of disease progression or remission and often can be rapidly de- termined in accessible biological fluids using facile modern assays. Sequential measurement of biomarkers, in turn, can expedite and facilitate the clinical trial process, thereby reducing the burden of assessment of traditional endpoints. However, the predictive value of biomarkers for clinical outcomes is frequently questioned, and a high level of proof is often demanded for their acceptance in clinical trial endpoints as opposed to time-honoured monitoring in clin- ical practice. Improved scientific methods are thus needed to select biomarkers for disease assessment from an often-overwhelming array of potential biomolecules whose abundance is known to be altered as a subsequence or consequence of the pathogenesis of a given condition. Phase 3 of clinical development The final and most extensive stage of the evaluation of putative new therapies in clinical trials seeks to elucidate whether the experi- mental therapy is safe and effective as intended for use. Phase 3 trials are typically completed in a randomized controlled design in which patients are randomly assigned to receive the experimental therapy or a placebo or in some situations, an established, active therapy. These studies are typically double-blind, that is both patients and doctors or sponsor are unaware as to which treatment is being ad- ministered. Once the trial is completed, the sponsors will assemble a large package of data to be submitted to the regulatory authority for review. Regulatory review in Europe can take usually about one year: in this time, the authorities are charged to make a determin- ation about whether the benefits of a new therapy outweigh the risks, for if so, the novel therapy can be approved for marketing. Phase 4/Postmarket surveillance Once a new therapy has been approved for marketing and distribu- tion, sponsors and public health authorities will continue to monitor patients for adverse events. Postmarketing studies may continue for years and new data may emerge that requires regulators to recon- sider the benefit-risk determination (Fig. 2.9.2). Expanded access/named patient treatment/Compassionate use Some patients facing acute, life-threatening diseases, may seek out experimental treatment outside of the normal clinical trial process for unapproved therapies. This increasingly common scenario is referred to as 'compassionate use' or 'expanded access' or named patient treatment. In many cases, the impetus to obtain access to experimental treatments

is patient-driven and typically deployed as a final or ‘last-ditch’ therapeutic measure. The increasing complexity of the regulatory process and with it, the prolonged development period for many drugs, has had consequential effects on patients with deteriorating health. Delays in the development process can cause an emerging a crisis in patients suffering from the effects of severe and progressive diseases, and has led to calls for earlier access. This state of affairs applies particularly to drugs for patients with life-threatening conditions where the risk of adverse and unwanted effects becomes less of an ethical concern. Advocacy groups sup- porting patients in such a position are exploring various options to enable patients to obtain access to an experimental drug (ostensibly with appropriate clinical surveillance and a practical framework for its administration). The difficulty with this worthy principle is that

2.9 Engaging patients in therapeutic development 121 the clinical development process alongside regulatory approval is in- tended to protect patients from unnecessary risks. In the United States, the number of requests for expanded ac- cess to experimental therapies, a process regulated by the Food and Drug Administration, increased from 1014 in 2010 to 1873 in 2014. This burgeoning, and international trend poses several chal- lenges for patients, the biopharmaceutical industry, and regulatory bodies. The complexities of these interdependent relationships are particularly exposed in instances when patients, their families and advocacy groups deploy large-scale social media campaigns to pressurize companies into providing early access to experimental therapies that are still in development and under regulatory scru- tiny (see Box 2.9.1). Patient groups partnering with industry to fund drug development Cystic fibrosis is an inherited genetic disorder caused by a muta- tion in the cystic fibrosis transmembrane regulator gene, CFTR; the disease causes progressive damage to the respiratory and digestive systems (see Chapter 18.10). One of the leading patient groups is the Cystic Fibrosis Foundation (CFF), which began funding spe- cific drug development efforts in the late 1990s with investments in a biotechnology company called Aurora Biosciences. In 2001, Aurora was acquired by Vertex Pharmaceuticals and received continued in- vestments from CFF that would prove vital in sustaining the risky cystic fibrosis research programme. This programme would go on to develop a novel pharmacological chaperone therapy, Kalydeco, which was approved for marketing in the United States in 2012, and was the first approved drug designed to treat the cause of cystic fi- brosis as opposed to symptoms. The Foundation will receive a one- time pay-out of $3.3 billion (US) in exchange for the rights to the royalties from the drug. This scenario represents a novel paradigm for funding drug development for a rare disease. CFF is utilizing those revenues to continue investing in further cystic fibrosis re- search and treatment. Patient engagement in drug development:
Disease burden, disease measurement,
and benefit-risk Unravelling the true burden of disease requires close input and collaboration with patients. This is especially true for diseases PHASE I TENS HUNDREDS NUMBER OF VOLUNTEERS THOUSANDS NDA/BLA SUBMITTED APPROVAL PHASE II PHASE III PHASE IV Regulatory approval POST-APPROVAL RESEARCH & MONITORING CLINICAL TRIALS REVIEW BASIC RESEARCH DRUG DISCOVERY PRE- CLINICAL POTENTIAL NEW MEDICINES IND SUBMITTED Fig. 2.9.2 The contemporary clinical development process. Box 2.9.1 Case study: Josh Hardy One recent and widely publicized case involved Josh Hardy, who had experienced severe health complications stemming from a rare kidney cancer. After a bone marrow transplant, Josh was infected by an adenovirus that, if untreated, would probably result in death. However, the patient’s responsible physician at St. Jude Children’s Research Hospital recognized that an experimental therapy, brincindofovir had the potential to treat the infection. Chimerix Inc., the company that was

developing the treatment, refused to provide access, citing concerns about cost, workload, and sustain- ability of such requests: ‘The company says helping him will slow efforts to get it on the market …’, as reported by CNN. Chimerix argued that as a small 54-person company in Durham, North Carolina, diverting their resources to this one case could inhibit their broader effort to get the drug approved as quickly as possible. What followed was a social media firestorm, with thousands of emails, Facebook, and Twitter messages being directed to the com- pany Chief Executive Officer, Dr Ken Moch, and other employees imploring them to ‘Save Josh.’ The company also reported receiving more extreme messages, including death threats. Ultimately, the company relented and with the engagement of the Food and Drug Administration created a new clinical trial to enrol Josh as the first patient rather than provide the treatment through the expanded access pathway. Josh responded well to the treatment and did well for 2 years but later declined and died due to other causes in 2016.

122 section 2 Background to medicine that may not be well-established in the medical literature, as many assumptions or clinical dogma may turn out to be unfounded or tenuous after further investigation. Disease burden is particularly poorly understood in rare diseases in part due to the limited op- portunity for surveys conducted by investigators, and the failure to invest in tools for measuring disease. Patient engagement in rare diseases is now almost the rule as patient groups fund and develop surveys of disease or natural history studies. The Cystic Fibrosis (CFF) Foundation is one example of an organization that established a network of centres of excellence, developed common methods for measuring and tracking cystic fibrosis (CF), and pub- lished information on the disease that helped all investigators or sponsors considering development treatments. This work has suc- cessfully supported efforts to develop new treatments for CF. Many other rare disease groups are replicating this effort to some degree, and developing data on their disease in the precompetitive space so that diverse therapeutic avenues, predicated on deep phenotyping and extensive clinical knowledge, can be explored. The increasing use of computerized international disease registries has had a useful effect in this field. Quantifying disease severity Disease measurement is one of the more complex areas of de- velopment; and patient groups alone are not usually able to pro- vide all the information concerning clinical measurement or patient-reported outcomes. Here an important synergy can de- velop, based on consultation and collaboration with experts who are able to develop quantitative instruments. These activities are expensive and often there is a need for industrial sponsor- ship to facilitate completion of such enabling work. Challenges in obtaining access to these data as public resources has led to more efforts to assure that all such natural history data sets do not end up as proprietary information of corporate sponsors, but are available for anyone working on a new treatment or develop- ment of tools. Determination of the true benefit-risk assessment for any treat- ment requires comprehensive understanding of the risks of un- mitigated disease and a deep appreciation of the trade-off between one disease risk and another risk—that which emanates or might emanate from the treatment. In the past, industrial sponsors and regulatory authorities spoke for the patients: it is now clear that there this tradition is an unwarranted presumption that lacks any depth of understanding about the experience of a chronic severe disease or indeed what patients, often supported by their families and the larger disease-family are willing to do to contribute to the management of their disease and future therapies. A recent example of patient engagement has been the work of a Duchenne muscular dystrophy patients’ group in the United States, called Parent Project Muscular Dystrophy (PPMD). Duchenne muscular dystrophy (DMD) is a genetic disease that leads to severe loss of muscle bulk and function. Males with the disease typically live

into their late twenties. In 2014, PPMD, convened a variety of stakeholders from throughout the Duchenne community and de- veloped a comprehensive survey tool to rigorously capture the key aspects of benefit:risk. One critical finding was that most parents would support a treatment that stabilizes their child's strength for one more year at the cost of one less year of life. That is a trade-off that would not normally be expected and, in most instances, runs not only counter to the usual traditions of professional ethics and decision-making, but also provides an unexpected foil to the con- ventional view of what patients really want. After the outcomes of this survey were disseminated, a broad co- alition was assembled, including parents of DMD patients, DMD patients themselves, academic researchers, and physicians, as well as representatives from the biopharmaceutical industry to discuss the implications for the development of treatments. The outcome of this collaboration was a guidance document that explores key areas for drug development including: benefit-risk assessments, diagnostic tools, natural history studies, clinical trial designs, and outcome measures including the use of biomarkers. Ultimately, this document was submitted to the Food and Drug Administration for consideration and was incorporated in part as an official guidance; it provides a practical roadmap for the biopharmaceutical industry as it seeks to pioneer useful new treatments. Conclusions Successful treatment of patients is at the heart and goal of medi- cine but the increasing complexity of treatments and under- standing of diseases has led to a beneficial societal metamorphosis which involves patients at all levels of therapeutic development. Including patients throughout the process of drug development enhances understanding of pathogenesis, measurement, and the personal impact of disease; genuine participation focuses attention on the authentic therapeutic targets of the disease. In summary, increasing involvement of patients and cognate organizations and advocacy groups broadly in drug development, has driven important changes to the regulatory process and almost always expedites achievement of the common goal to deliver safe and salutary new therapies.

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