The Promising Revolution of Participant-Led Research in Rare Neurological Diseases; Potential Benefits and Pitfalls

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Summary

Increasing access to online sources and social networks are changing the environment of rare diseases research. Patient- and parent-networks use these new resources not only to access health information but also to initiate and conduct research. Using current examples of patient or parent-led research (PLR) beyond clinical research, we summarize and discuss potential benefits and pitfalls of PLR.

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Keywords: Participant-led research, research ethics, crowd funding, citizen science, best interests of the child, parental autonomy

La révolution prometteur du "participant-led research" sur les maladies neurologiques rares; Avantages et les pièges potentiels

Accroître l'accès aux sources en ligne et les réseaux sociaux sont en train de changer l'environnement de la recherche sur les maladies rares. Réseaux de parents et patients utilisent ces nouvelles ressources non seulement d'accéder aux informations de santé, mais aussi d'initier et de mener des recherches. En utilisant des exemples actuels de recherché conduit pare les patients ou parents (participant/parent-led research, PLR) au-delà de la recherche clinique, nous résumons et discutons des avantages et les pièges de PLR.

Mots clés : Participant-led research, éthique de la recherche, financement par la collectivité, citoyen scientifique, autorité parentale, intérêt supérieure de l'enfant

Die vielversprechende Revolution von "Participant-Led Research" in seltenen neurologischen Erkrankungen: Mögliche Chancen und Probleme.

Der deutlich erleichterte Zugang zu Informationen via Internet und Netzwerke verändert das Umfeld für Forschung zu seltenen Krankheiten. Patienten- und Elterngruppen verwenden die neuen Möglichkeiten nicht nur als Tor zu gesundheitsrelevantem Wissen, sondern auch um Forschungsprojekte zu fördern, zu planen und durchzuführen. Mit Hilfe aktueller Beispiele von Patienten- und Eltern-geführter Forschung beleuchten und diskutieren wir die daraus entstehenden Chancen und Probleme.

Schlüsselwörter: Participant-led research, Forschungsethik, crowd funding, citizen science, im besten Interesse des Kindes, Elternautonomie

"[The health care service] of the future will be one of patient power, patients engaged and taking control over their own health and healthcare."
Gordon Brown, Former U.K. Prime Minister (cited from Swan 2008)

Introduction

Epilepsy and epilepsy syndromes belong to the most common neurological disorders. The underlying cause, however, remains obscure for a large portion of patients [1]. The focus on functional and molecular mechanisms in etiologic research shares a common denominator with other rare diseases [2]. While each rare disease is rare, taken together they are common. Estimations range between 27 to 36 million people affected in the EU by a spectrum of 5000 to 8000 distinct rare diseases [3]. These patients are particularly exposed to the global crisis in drug development with exponentially rising costs after the discovery and development of new pharmaceutical drugs has plateaued

(so-called "low hanging fruit" principle). In response to this development, treatment and research centres for rare diseases are being established [4].

However, despite great efforts in forming networks of specialized centres, and despite tremendous general advances in biomedicine, rare diseases and rare neurological disorders in particular remain an area where therapeutic progress has been slow. There is still a great need for basic and translational research in rare diseases. Currently there are six stakeholders, which propose, enforce and initiate research projects on rare disease: The research institution (1), advocacy groups (2), patients and their families (3), health care professionals (4), funding bodies (5) and the state (6). In recent years legislative incentives in both USA and the European Union have stimulated research initiatives and the formation of networks, including projects particularly focusing on rare neurologic diseases (e.g. http://www.eurordis.org/content/european-network-rare-paediatric-neurological-diseases-neuroped or http://www.epilepsy.com/ren). However, more consorted efforts are still needed. Our article focuses on the new movement of systematic efforts by patients, their families and advocates in doing research, also called patient or parentled research (PLR).

Patient or parent-led research (PLR)

Patients, their families and advocates have in the past often come forward to fill the research gap. Advocacy groups typically drew attention to their particular needs and associated research questions; medical professionals and scientists subsequently developed, initiated, and coordinated particular research projects and registries, while patients and their families were involved throughout different phases within this process [5].

Recently, however, the scientific landscape of rare diseases has begun to change: The increasing access to online sources such as social networks and knowledge databases has given rise to the formation of online communities that share common interests [6 - 8]. Today, patients network connect online easily and more globally than ever before [9]. They use new media not only to access health information and exchange experiences, but also to initiate and conduct health research. Approaches by these new communities include self-experimentation, self-surveillance, analyses of genetic information, and genome-wide associated studies (GWAS) [10, 11]. As a consequence, there is an increasing number of "crowd sourced", "citizen-driven", "participant-centric", or "participant-led" projects supported by non-profit as well as commercial organizations like CureTogether, DailyStrength, MedHelp, HealthChapter, MDJunction, Experience Project, Peoplejam, and OrganizedWisdom [12, 8, 13]. Health research, initiatives appeal to large numbers of people to collect funding, which is then dedicated to a particular research project. There is a proliferation of web-based platforms, which aim to facilitate such initiatives [8, 13, 14]. Almost 10'000 persons with epilepsy currently share their data including clinical and therapeutic details on patientslikeme.com (https://www.patientslikeme.com/conditions/3-epilepsy).

The parent funded Citizens United for Research in Epilepsy (CURE) has recently launched a patient led project called Epilepsy Genetic Initiative with the aim of uncovering the causes of epilepsy, develop precision treatments and design possible cures (http://www.cureepilepsy.org/research/). Such patient- and parent-led research (PLR) has been enabled through crowd-funding.

All these new, so-called bottom-up initiatives are testing the ethical and regulatory limits within which clinical research has traditionally operated [15]. These efforts have yielded some interesting results and at the same time they have raised some ethical questions.

Current examples of PLR beyond clinical research

Research conducted within PLR includes self-surveillance, self-experimentation, analyses of genomic data, and genome-wide association studies (GWAS) [16]. To give an idea of the powerful spectrum of PLR we describe two examples. Although there are currently only few PLR studies concerning epilepsy, we believe that PLR has the potential to support and create similar activities for rare forms of epileptic diseases and it will be only a matter of time before patients with epilepsy or their parents will ask for these emerging possibilities.

Example 1: Amyothrophic Lateral Sclerosis (ALS)

Back in 2007 a little-noticed Italian news report was about a small trial, suggesting that lithium may have a beneficial effect for patients with ALS. A patient translated the story with the help of Google and informed other patients with the help of social networks including the online platform PatientsLikeMe. Within 6 months after publishing a small study of 16 patients treated with lithium 160 patients reported obtaining lithium off-label and tracked their health-related data on Google Spreadsheet including a validated functional rating scale. PatientsLikeMe further added tracking of lithium blood concentrations, data entry reminders, and installed support by nurses to respond to side effects. Results (with negative findings) of this randomized controlled trial were openly available within nine months followed by a longer-term follow-up report (with the entire anonymised dataset as supplementary material) [17]. A formal publication in the journal Nature Biotechnology appeared as well.

Example 2: Niemann-Pick Type C

Researchers and families of young patients with the rare disease Niemann-Pick Type C (NPC) currently face a remarkable problem, which is the fruit of years of adamant patient activism: Three companies are just launching three different clinical trials with new promising therapies at the same time. The current problem is, that the pool of eligible patients is too small to gain significant data for all trials, which again leads to uncontrolled competition between companies, investors and communities. While families fear to "lose out on having an approved treatment", they have the preference to participate right away in the most promising trial or to choose compassionate use of an unstudied therapy in fear that they won't be among the randomized or eligible participants to receive the drug. As a result there remain even less patients eligible for one of those trials [18]. In this context the journalist Amy Marcus reported an impressive and compassionate story about 9-year-old twin girls affected by NPC including their parents' odyssey and efforts as "citizen-scientists" by starting to use, to promote and to test a formerly unapproved therapy (cyclodextrin). While the federal drug administration raised concerns about potential side-effects, the parents started to administer cyclodextrin, analyse and record urine and blood levels of their daughters by themselves and shared their experiences with others. Their efforts finally culminated in a NIH-trial and a subsequent involvement of a pharmaceutical company, which before – due to financial considerations – did not show any interests in such a trial before the parent/patient-led research [19].

Promised benefits of PLR

Several benefits can be derived from PLR with perhaps the most profound being that individuals are enabled to become more actively involved in their own health. The positive effects can be seen from a value-oriented and result-oriented point-of-view (**Table 1**). From the perspective of values PLR promises to realise the basic human right of participation in scientific research [20]. Moreover it fosters an equal and substantial partnership between all stakeholders, such as patients, health care professionals, researchers and industries, which may be less constrained by geographical, financial or cultural barriers than conventional research. Commercial organizations such as PatientLikeMe or 23andMe have the potential to incorporate different roles and aims from all kind of stakeholders by supporting patients in collaboration with advocates, scientists, private donors/investors, industries, governments etc. From an outcome-oriented perspective PLR can help support, generate, personalize as well generalise health knowledge. It can open an innovative marketplace, which fosters new connections (including funding) between previously unrelated sources and, if trials are made transparent, participants and others will be informed faster about positive or negative effects of a certain treatment or intervention independent of other stakeholder's interests [21]. Especially negative findings like new side effects can be discussed openly and benefits can be judged and weighed by patients or parents in terms of their individual needs and values. Moreover mechanisms like social networks, crowd-funding, and public recruitment of participants can facilitate diagnosis, trial enrolment and treatment for a a larger patients group. It also may thereby help

Table 1: Advantages of using and promoting PLR

Promised Benefits
Value-oriented perspective
• Participation by having a greater voice in medicine
• Substantial and equal partnership between all stakeholders
• Foster adequate reflection of perspectives and input of citizens.
• More accurate priorization of outcomes patients and families truly value
• Translating trial results to the "real world" of patients and families
Outcome-oriented perspective
• Enabling research in unfunded or underfunded areas
• Producing generalisable health knowledge
• Benefit for a bigger number of patients
• Benefit for the wider society
• Easy and better recruiting/enrolment of participants
• Deliver results about positive and negative effects more rapidly
• Greater self knowledge

society at large by supporting patients and families to achieve greater (self) knowledge and increased responsibility for their own health and their health promoting behaviour.

Emerging ethical questions and problems with PLR

While the potential of patients' communities and their involvement in the rare disease research agenda can play a catalytic role in the development of diagnostics and treatments, they certainly do pose a new set of ethical questions: How can PLR comply with rigid scientific standards, which are needed to add relevant and useful data to the standard scientific community? And how can PLR be conducted ethically? **Table 2** gives an overview of identified ethical problems related to PLR. Basically the ethical questions arise from (potentially) harmful decisions or actions (1), failure to render (optimal or necessary) assistance (2), injustice (3) or disrespect of autonomy (4). Different questions and problems do concern stakeholders in different ways. While parents may struggle with multitude of promising but uncertain therapy options, researchers, health care professionals, sponsors and the state have to reason about their responsibility and duty regarding patients and their parents. How should clinical research institutions respond to parental requests about organizing a research project involving their children, i.e. suggesting an off-label use of a drug? How should institutions respond to parental requests for data-sharing with other researchers or bottom-up online research projects? How should medical professionals, searching for new therapeutic and diagnostic methods, respond to the methodological challenges of these new research forms, including self-selection and self-reporting of symptoms or phenotypic data [16, 22]. In particular, what additional risks may such initiatives carry for children when they are involved in projects that have not gone through the standard research review systems? For example, PLR bypasses control mechanisms, which ensure enough preclinical evidence before launching clinical trials.

PLR changes not only the structure of research but also the relationships between all stakeholders involved. It may undermine current mechanism for protecting patients, researchers and funding bodies including the traditions research system, that are aiming to ensure reliable medical evidence (and subsequent confidence) [23]. So finally the questions culminate in how the energy and the potential of those initiatives can be harnessed and steered to fill the large gaps in clinical rare disease research.

There are currently neither consensus nor common guidelines, which help stakeholders to deal with these questions.

A way forward

Keeping the presented benefits and pitfalls in mind clinicians and standard research institutions have to develop responsive mechanisms to these new initiatives. Such mechanisms should aim to foster partnerships between these communities and the standard

Table 2: Emerging ethical questions and problems with PLR

- Lack of/uncertainty about adequate information and consent/assent in terms of potential harm and alternatives
- Limits of parental authority in enrolment of their child in PLR
- Endangerment of traditional social values such as dignity, privacy and justice
- Inadequate and/or unnecessary risks by self-experimentation
- Peer pressure to participate in trial
- Exploitation of vulnerable individuals in desperate search of help
- Bias and distortion arising from the use of self-reported and self-collected symptoms and data
- Bias by heterogeneity of participants
- Lack of overview and difficult regulation of PLR by heterogeneity of participants
- Blurring boundaries between treatment, self-experimentation and life-style driven enhancement
- Missing acceptance of PLR as an authentic mode of research: obstacles in conducting research and publishing results
- No regulations concerning quality control and security by undermining current state-of-art concerning professionalism and ethics
- Uncertainty how to use results of PLR in terms of validity and evidence in clinical therapy
- Study enrolment with risks of harm in the light of inadequate methodology

Table 3: Accompanying measures and responsive mechanisms

- To („creatively") apply existing legal frameworks
- To gain a deeper understanding of available possibilities and current practices of PLR
- To comprehend that different activities within PLR may require different procedures
- To accept research issues outside of the scientific mainstream
- To promote shared decision-making amongst stakeholders
- To recognize PLR as a valuable means of contributing to generalizable health knowledge
- To provide material support for PLR, incorporating its outputs in standard research
- To support reciprocal responsibilities of all stakeholders
- To establish uniform ethical and scientific standards
- To distribute publicly accessible set of standards for its oversight
- To support „transparent" and „open" manner of communicating about study design, results and their meaning
- To develop an online platform where PLR activities may be publicly registered
- To provide scientific advice on research proposals through publicly funded panels of experts
- To create online tools, including scientific and ethical checklists of relevant considerations
- To develop journal appraisal systems that are known to be receptive to submissions of results from PLR.
- To foster ongoing dialogue about benefits, pitfalls and responsive mechanisms

scientific establishment while ensuring that ethical standards are respected. Scholars have only begun to study these new challenges and recent work has offered recommendations for how participant-led research can be ethically conducted [20, 24]. **Table 3** gives an overview of some accompanying measures to implement PLR. In general PLR seems to have arisen largely in reaction to the seclusion of science in the 'ivory tower' of science and regulation that despite its spirit has stifled innovative research [25]. In combination with the lack of a broader research agenda for a specific rare disease and the lack of any treatment, there is a strong interest of parents to seek out research projects, to fund some, some, or to generate research projects involving their sick children. Therefore, a "top down" regulation deriving from established institutions seems unlikely to be successful. The most promising way seems to use the language and culture, which PLR is just establishing by : directly engaging with the affected community [17, 25]. Existing legal and ethical frameworks can help to address some of the ethical challenges in PLR: e.g.Interference with parental authority is justified and required if children were exposed to significant harm [20]. But neither existing ways of communication, nor currently operating ethical and legal review boards seem to be sufficient for this new task. The question of how to define "significant" harm has to be answered on individual basis as most situations in PLR are unique and have no precedent. Second, PLR activities do not have yet a clear control mechanism and may have no incentives to restrict their newly gained possibilities by such a mechanism. Third, existing control mechanisms (such as ethics review committees, IRBs) may have limited capacities and mandates for providing oversight to PLR activities.

While PLR activities need societal acceptance of their role and of their added value despite being outside of the scientific mainstream, they also need clearly defined standard for high scientific research quality [23]. Mutual responsibilities that address the needs of different stakeholders should be discussed and defined within the public domain[20]. For example, to provide scientific advice on research proposals, existing agencies could foster publicly funded panels of experts [23].

Finally established researches and research institutions should help to develop journal appraisal systems that are receptive to submissions of results from PLR. As a result such journals in addition to existing online communities can help to foster an on-going dialogue about benefits, pitfalls and further responsive mechanisms (more detailed steps listed in **Table 2**).

It is likely to expect that patients and their families dealing with disease will have increased scientific understanding and subsequently will feel confident to take more responsibility for research and implementation of research outcomes in practice [26]. In our opinion there is neither a way nor a reason to suppress this on-going revolution but it is now the time to think critically and creatively about how this can contribute to better scientific research and ultimately to a better and more just health care.

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