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Patient Registries for Neurodegenerative Diseases: Approaches for the 21 Century

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ABSTRACT

This Review Article summarizes the different modalities of disease registries and which ones are most appropriate for the identification of early disease stages or even prodromal individuals for the enrollment in disease-modifying trials. It provides some recommendations which Disease Registries may enhance the success of patient recruitment in the future, namely a mix of paper and web-based patient-powered registries with various feed-back mechanisms.

Keywords: Patient-Powered, Registry, Neurodegeneration, Clinical research, Recruitment

Background

Even though over 80 novel therapies were tried in Alzheimer's in the past decade, all failed so far [1]. That leaves the question whether the therapeutic targets (amyloid, BACE, gamma-secretase) were wrong – or whether a methodological mistake is underlying that series of failures [2].

Amongst the ideas what errors may have contributed to the given situation, the concept came up that any disease-modifying therapy needs to start earliest possible in the disease process to preserve a sufficient amount of neuronal cells for proper functioning.

Implementing this concept in clinical trials leaves the question: how to identify individuals that may develop a disease in coming years, but not yet have symptoms and – as a consequence – are not aware of the fact they could benefit from the participation in such a trial (Figure 1).

A second question is related: how to motivate individuals to register and (what is even more challenging) to regularly update their registry-information who are not yet suffering from any symptoms? This question is critical since we know that only about 6% of patients with a severe disease participate in clinical trials [3]. How much lower will be the % in a population yet being symptom-free?

In Alzheimer's disease, a recent survey of Karolina Krysinska, et al. [4] revealed 31 ongoing AD registries across the globe. More than half of the registries aimed to conduct or facilitate research, including preclinical research registries and registries recruiting research volunteers. In the USA, 5 registries were identified which were exclusively built to facilitate the enrollment of prodromal or early stages of the disease [5].

The contribution of registries to the operational success of clinical trials in AD is not easy to assess. Based on limited publicly shared examples [5] only a very minor percentage of registered individuals would actually qualify for the enrollment in an early symptomatic AD study. In a selection funnel hypothetically applied to the Brain Health Registry, out of at that time 31,428 registered individuals, only less than 10% fulfilled certain common selection criteria such as age, cognitive state, no prohibited concomitant medication and willingness to participate in a study. When also the criterion of yet observed cognitive deficits was applied, even less (only 144 individuals = 0.5%) would be eligible. This rate was confirmed when later actual

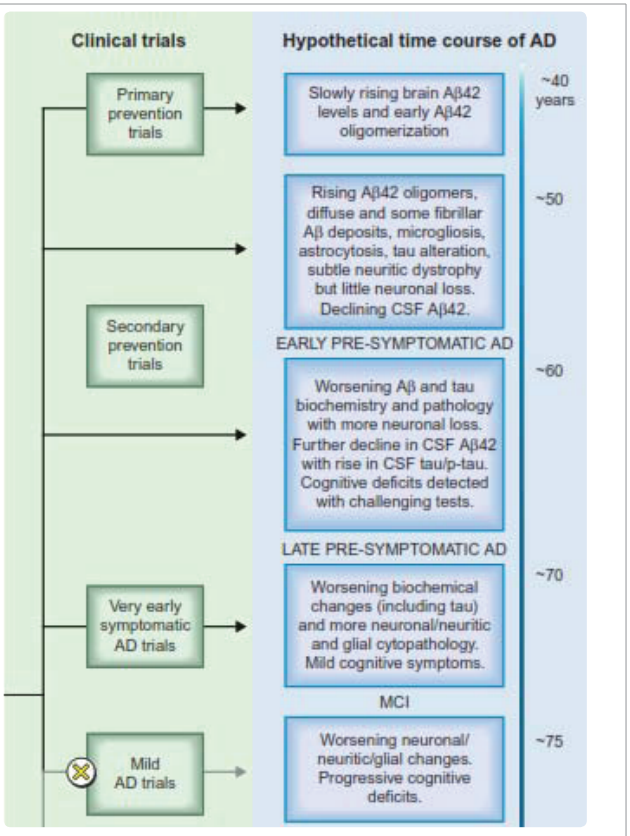

Figure 1: In the most common neurodegenerative disorder Alzheimer's, the disease starts decades before the first symptoms become obvious. Currently Mild AD studies are conducted but the first "Very early symptomatic AD trials" are ongoing. For the recruitment in such "very early" studies, special recruitment tactics are needed [2].

studies were supported by this registry. As detailed in [6], the vast majority of patients (98.5%) participating in clinical studies are still identified by the participating centers through local advertisement and other established methods: In four interventional Phase 2 and 3 (pre-marketing) clinical trials in AD, a total of 1,387 individuals out of the total registry of 53,782 datasets (2.6%) were referred to these studies, with only 21 being ultimately enrolled (1.5%). This raises the question whether registries are at all an appropriate method to enhance enrollment.

In other neurodegenerative diseases, registries are not yet as common as in AD. In 2015, the EU Joint Programme Neurodegenerative Disease Research (JPND) reviewed the registries in Alzheimer's disease, frontotemporal dementia, Huntington's disease, Parkinson's disease, prion disease, motor neuron disease and the spinocerebellar ataxias. In all entities only local registries were in place, except in Parkinson's. This creates the questions whether and under what conditions it would be worth an investment in patient registries for expected disease-modifying studies also in these disease entities.

Method

We reviewed existing literature which detailed the impact of registries on subject enrollment in disease-modifying neurodegenerative trials. Since only limited publications are yet available in this field, we also utilized internal insights from ongoing clinical trials at ICON, and from existing stroke registries and the currently established 'Digital Dementia Registry Bavaria' (digiDEM; www.digidem.de) at the University Erlangen-Nuremberg, to identify best practices.

Results

Registries are defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s) [7,9].

Various guidance exists for the proper set-up of a registry [7,8,10,11].

According to Workman TA [12] one should mainly differentiate between:

1. Research-centric; these can be further divided into

- Population-focused / -based registries (enrolling a more representative national or regional sample of the population, also often named a "cohort"). These are often closely linked to the national public healthcare system and re-embursement, such as in the Swedish SveDem which reached a national coverage rate of enrolling 30% of newly diagnosed patients with AD in 2012. Another example where the reporting of patients in a registry is a mandatory requirement is the California Parkinson's Disease Registry [www.capdregistry.org]. Also patient-empowered registries are most typically population-focused, such as the Michael J Fox trial-finder registry, also in PD.
- Hospital based databases. These are often more selective, thus potentially having to some degree a selection bias.

However, when managed by researchers, the registry may provide little or no opportunity for involvement or control by patient or family members or patient support and advocacy organizations. As a result, the registries may not meet the needs of patients, family members and informal caregivers as well as advocacy groups [12,13].

Logically, that would limit the ability of these registries to be of interest for the targeted population. The alternative is:

2. Patient-powered registries [8]. These ones are in many ways similar to researcher-generated patient registries, with one exception: patients and family members, not researchers, "power" the registry by managing or controlling the collection of the data, the research agenda or the data, and/or the translation and dissemination of the research from the data. An effort to document such patient-generated registries is being undertaken by the American Association for the Advancement of Science through funding by the Agency for Healthcare Research and Quality [14]. A study of 201 disease advocacy organizations found that forty-five percent had supported a research registry or a biobank [15].

This differentiation is relevant since it not only is determining what group initiates the registry (academia versus patient groups), but also to what objectives are fulfilled.

Academic, research-centric registries are mainly interested in:

A. Facilitate the recruitment of patients for clinical trials. Johnson, et al. [16] provide a good overview what methods of enrollment in a disease registry work best. Direct mailing turned out to be most expensive but of limited effect, while paid internet advertisements (Facebook and Google) were most effective and yielded over 65% of all enrolled individuals. Indirect methods (word of mouth, twitter, advocacy websites) were contributing only about 15%. The most promising method however depends on the age group, with those above 65 years still prefer classic direct mailing [17].

B. Epidemiology: Learn about population behavior and their association with disease development.

The patients are more interested in aspects such as:

C. Current information about their disease

D. Support the development of new therapies

E. Empowerment to better manage their chronic disease.

There is of course overlap of objectives between both groups. The key question: Which of these objectives are crucial to be addressed for the success of registries which shall facilitate enrollment in early disease treatment studies?

Individuals entering such registries do that in general if three conditions are fulfilled [17].

1. For altruistic reasons; patients expect their contribution may help others. Regular (e.g. bi-annually) status reports shared with all stakeholders (including all registered participants) are a good tool to ensure this aspect is fulfilled. An example for such a status update report is provided by the Cystic Fibrosis Foundation [18]. Another option to address that need is the ability of members to not only participate in top-down shared information, but also to communicate bottom-up or even horizontally with the peer group. The patient-powered registry "patientslikeme" fully implemented that requirement (Figure 2).

2. Insights and access to new therapies; they expect their own care may benefit. This aspect is detailed by Nelson, et al. [19]. The result could be a win-win for both key stakeholders (health care providers and patients) by mutually providing status updates as outlined in Figure 2.

3. Convenience; enrolling in a registry must be easy. For that purpose, a number of technical solutions are available, mainly to register online. This however creates the risk of duplicate or even falsified entries, what led to the concern that "only a small minority of patients with sufficient education and ability are able to participate, and that data may be biased" [20]. However, for registries exclusively focusing on the pre-identification of individuals at risk, this is much less an issue than for registries which shall generate epidemiologic data or even support a drug registration. Also, limiting competition and reducing the fracturing of efforts to collect data, raise funds, or advance knowledge is a relevant aspect of convenience. However, until such "best practices" registries are not yet fully in place, competition for best solutions should not be restricted.

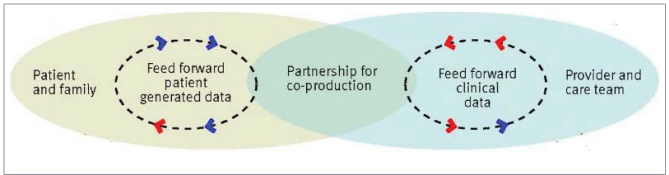

Figure 2: Both main stakeholders use the registry as a platform to share and exchange information relevant for both of them. Modified from Nelson, et al. [19].

In such shared models, a fourths aspect is of relevance, more in Europe than in US: Data privacy; make sure any data provided are only used for the detailed purpose and otherwise safe.

Another item that should be kept in mind when setting up a registry is the appropriate data structure. Such a default data structure is detailed in [21]. For a patient-powered registry we propose the following most lean structure:

Basic data

- The consent for the registry and data use (by patient and legal guardian; of growing relevance is the upfront provided consent while the patient is still capable of consenting for activities, e.g. participation in trial or in any biosampling, what may only happen after disease progression)
- Patient diagnose
- Patient personal information (name, gender, date and place of birth)
- Disease history (age at onset and at diagnose)

Epidemiology

- Familial or sporadic
- Genes identified (if any)

Clinical status

- Treatment
- Symptoms

Research status

- Agreement to be contacted for a trial
- Agreement for specific procedures (CSF sampling, biosampling, MRI, PET)
- Having already given a biologic sample

Since not all registries follow a consistent format, it leaves the weakness that an aligned approach which would use all existing registries in a similar fashion is not possible. However, in large clinical trials in AD, targeting the enrollment of sometimes over 1,000 participants in Phase 3 studies [22], a harmonized approach would make contacts more efficient.

A fully compatible data structure may however become less and less relevant due to the improving abilities to perform data-mining in various databases [23].

With IT technology progressing further, not only various registries may get linked, but also registries and biobanks and/or Electronic

Health Records (EHR). EHRs may thus supplement the current role of registries, even though they usually not allow a direct contact of the individual patient. Such links into other database formats would also open doors to the use of Patient Reported Outcome Data in registries. More and more patients use wearable technology through Smartphones. These may provide very conveniently captured information about disease onset and progression, as already done in Parkinson's [24] or in Alzheimer's [25].

Discussion

The implementation and maintenance of a registry which fulfills all these requirements is a major investment. For instance, in Australia, the cost of establishing a major national registry (50,000 cases reported annually), including the cost of the IT systems, has been estimated in 2013 at approximately US$ 0.5–US$0.75 million and the annual cost of maintaining such a registry at approximately US$0.75–US$1 million [26]. Such an investment to enhance enrollment in a disease-modifying clinical trial in a neurodegenerative disease should provide some appropriate return.

Patientslikeme.com managed to become a profitable registry with over 600,000 members in 2,800 different conditions. That may be due to the fact this registry is built bottom-up, i.e. a patient-powered registry which applies best practices to become an attractive and user-friendly tool that is not only collecting information but also offering ways to individually retrieve information from the system (Figure 3).

The concern around such "bottom-up" built registries is that only a small minority of patients with sufficient education are able to participate, and that data may thus be biased.

Furthermore, when collecting data from patients online, there is the distinct possibility that users are not who they appear to be. In registries which have the objectives B (Epidemiology), C (Learn about the disease) or D (Support the development of new therapies) it is crucial to have access to reliable data. If the only objective is A: Enhance enrollment, this restriction is less an issue, since fake entries would not respond to any request for participation, while anyway, only a small portion of the registered individuals qualify for a given study.

Such fake entries nonetheless may increase administrative efforts for the registry and also create unnecessary high failures during initial screening for a new study.

As a solution, many websites ask users to enter minimal information about themselves, thus lowering the barrier for misrepresentation [27].

Combining a registry with a bio-bank would nearly eliminate that risk, since every registered person would have to provide a bio-sample - such as in the for-profit registry 23andme.com.

Last not least, Smartphone-based technology would allow remote identification through scanned and securely transmitted identity cards, a technology already used by banks and for airline check-in.

- Thus, from the characteristics for the quality of a registry [11] only the below two items apply to the herein described Type A registries. A Governance layer (e.g. it should have a charter and defined oversight roles, and a business plan, all being publicly available) is required
- Data security for all registries capturing any type of privacy information.

Data quality and the information quality are less relevant (as detailed above).

Conclusion

Registries which shall primarily support the enrollment in preventive trials can be of a quite simple design, what should allow a

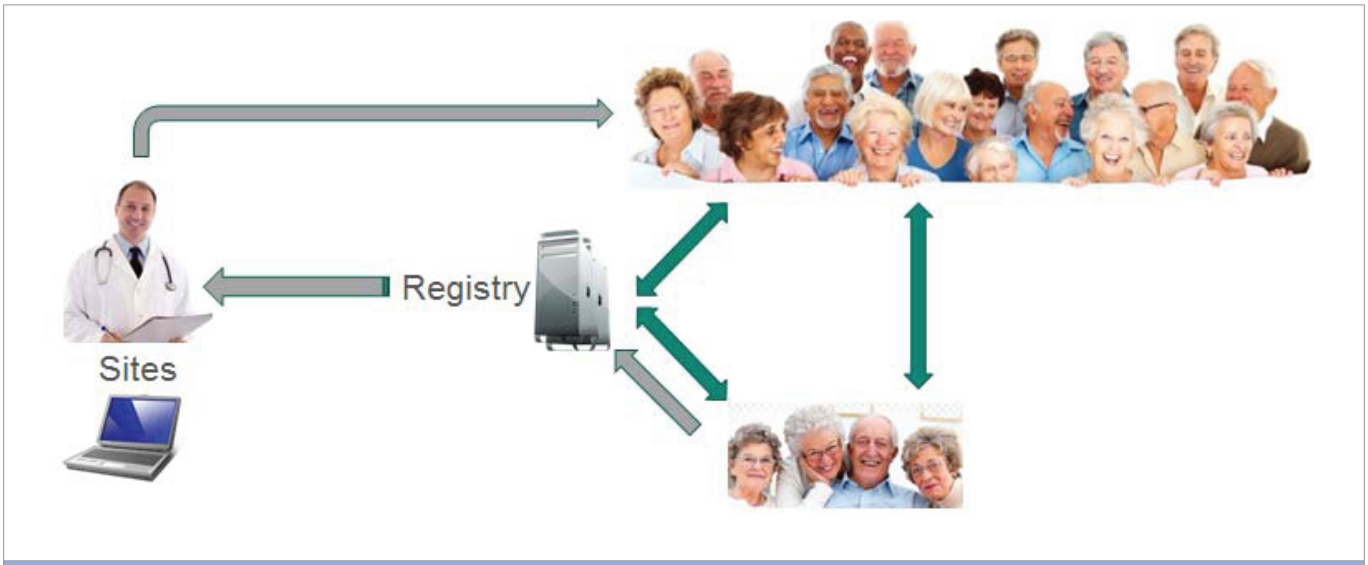

Figure 3: Registries with a focus on being attractive for registrants should not only collect information from the individual into the database in a "one way street" approach (grey arrows). Allowing the retrieval of information from the data-repository plus the exchange of information amongst the peer-group of patients such as informal caregivers, family members, advocacy groups makes a registry more attractive (green arrows), comparable to nowadays "social media".

rapid and large-scale set-up also in neurodegenerative diseases aside AD, such as Parkinson's (PD), Progressive Supranuclear Palsy (PSP), Multi-System Atrophy (MSA), Amyotrophic Lateral Sclerosis (ALS) and others. High compliance and retention can get achieved with a "patient-powered" design that also addresses the need for feed-back and interaction to / from and in-between the registered individuals. Modern IT technology should be applied to allow links into other similar registries and the integration of further data-sources, such as biobanks, Patient-Reported Outcomes and data from patient's Smartphone.

References

1. PhRMA analysis of Adis R&D insight database, June 2015
2. Schüler, P., Siegfried, K., Hüll, M. (2013) Lessons Learned from Major Clinical Trials Conducted Over the Past Decades. Global Clinical Trials for Alzheimer's Disease, 2014: 77-97
3. Getz, K. (2007) The Gift of Participation: A Guide to Making Informed Decisions About Volunteering for a Clinical Trial. Bar Harbor, ME: Jerian Publishing.
4. Krysinska, K., Sachdev, PS., Breitner, J., Kivipelto, M., Kukull, W., Brodaty, H. (2017) Dementia registries around the globe and their applications: A systematic review. Alzheimer Dement, 13(9): 1031-1047.
5. Aisen, P., Touchon, J., Andrieu, S., Boada, M., Doody, R., Nosheny, RL., et al. (2016) Registries and cohorts to accelerate early phase Alzheimer's trials. J Prev Alzheimers Dis, 3(2): 68-74.
6. Schüler, P. (2017) Presentation at 10th CTAD conference, Boston.
7. Gliklich, RE., Dreyer, NA. (2010) Registries for Evaluating Patient Outcomes: A User's Guide, 2nd edition. AHRQ Methods for Effective Health Care, 10-EHC049.
8. Gliklich, RE., Dreyer, NA., Leavy, MB., Christian, JB. (2018) 21st Century Patient Registries. Registries for Evaluating Patient Outcomes: A User's Guide, 3rd Edition. AHRQ Methods for Effective Health Care, 17(18)-EHC013-EF.
9. Zhang, S., Gaiser, S., Kolominsky-Rabas, PL. (2018) Cardiac implant registries 2006-2016: a systematic review and summary of global experiences. BMJ Open, 8(4): e019039.
10. Niederländer, CS., Kriza, C., Kolominsky-Rabas, PL. (2017) Quality criteria for medical device registries: best practice approaches for improving patient safety – a systematic review of international experiences. Expert Review of Medical Devices, 14-1: 49-64.
11. Zaletel, M., Kralj, M., Nagajne, M., Doupi, P. (2015) Methodological guidelines and recommendations for efficient and rational governance of patient registries: Metka Zalatel. European Journal of Public Health, 25: 3- ckv169.006.
12. Workman, TA. (2013) Engaging Patients in Information Sharing and Data Collection: The Role of Patient-Powered Registries and Research Networks. AHRQ Methods for Effective Health Care, AHRQ 13-EHC124-EF.
13. Ulbrecht, G., Gräßel, E., Nickel, F., Kolominsky-Rabas, P. (2018) Low-threshold consulting services for dementia: Quality criteria from a provider's point of view. Nervenarzt, 89(5): 516-523.
14. Social Networking and Online Health Communities: Identifying and Describing Patient-Generated Registries. 2012
15. Landy, DC., Brinich, MA, Colten, ME., Horn, EJ., Terry, SF., Sharp, RR. (2012) How disease advocacy organizations participate in clinical research: A survey of genetic organizations. Genet Med, 14(2): 223-228.
16. Johnson, KJ., Mueller, NL., Williams, K., Gutmann, DH. (2014) Evaluation of Participant Recruitment Methods to a Rare Disease Online Registry. Am J Med Genet A, 164A(7): 1686-1694
17. Solomon, DH. (2018) Determining the Best Methods for Using Patient Registry Data in Clinical Research. Patient-centered outcomes research institute, HSRP20143574.
18. Cystic Fibrosis Foundation (2018) Annual data report technical summary. Bethesda.
19. Nelson, EC., Dixon-Wood, M., Batalden, PB., Homa, K., Van Citters, AD., Morgan TS., et al. (2016) Patient focused registries can improve health, care, and science. BMJ, 354: i3319.
20. Frydman, G. (2009) Patient-driven research: Rich opportunities and real risks. J Participat Med, 1(1): e12.
21. EUCERD Joint Action. (2015) Minimum dataset for rare disease registries.
22. Luo, J., Weng, H., Morris, JC., Xiong, C. (2018) Minimizing the sample sizes of clinical trials on preclinical and early symptomatic stage of Alzheimer's disease. J Prev Alzheimers Dis, 5(2): 110-119.
23. Sernadela, P., González-Castro, L., Carta, C., van der Horst, E., Lopes, P., Kaliyaperumal, R., et al. (2017) Linked registries: connecting rare diseases patient registries through a semantic web layer. Biomed Res Int, 2017: 8327980.
24. Trister, AD., Dorsey, ER., Friend, SH. (2016) Smartphones as new tools in the management and understanding of Parkinson's disease. NPJ Parkinsons Dis, 2: 16006.
25. Mc Carthy, M., Muehlhausen, W., Schüler, P. (2016) The Case for Using Actigraphy Generated Sleep and Activity Endpoints in Alzheimer's Disease Clinical Trials. J Prev Alzheimers Dis, 3(3): 173-176.
26. Australian commission on safety and quality in Health Care (2014) Framework for Australian quality registries. Sidney, ACSQHC.
27. Frost, J., Okun, S., Vaughan, T., Heywood, J., Wicks, P. (2011) Patient reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. J Med Internet Res, 13(1): e6.