A tool for identifying long-delay trigger factors:
a significant potential for patients, clinicians and researchers

Challenger:

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Background: why is there a challenge?

A significant number of diseases and conditions are characterized by intermittent attacks or flare-ups which are (sometimes or always) triggered by provoking factors with a delay on the time scale of many hours or several days. This includes migraine, epilepsy, inflammatory bowel disease, multiple sclerosis, psychiatric disorders, muscle/joint pain, and others. This contrasts to disorders with a shorter trigger factor delay (e.g. minutes or an hour), such as asthma attacks and acute allergic reactions. Compared to such "short-delay" conditions, the "long-delay" conditions:

- Are less elucidated scientifically, because of the *less clearly perceivable and measurable* cause-and-effect relationship (e.g. compared to an airway provocation challenge).
- Are harder to prevent in the individual, because her/his specific trigger factors are harder to pinpoint, and in turn harder to avoid for the patient. As an example: When a migraine attack begins, it is hard for the individual to know e.g. if one of the many different food items ingested in the past 24-48 hours may have been responsible, if another trigger was at play (e.g. sleep disturbances, stress, dehydration, weather changes etc.) or if the attack did not have a specific trigger.
- Lead to more frustration, and sometimes despair, among patients, because of the powerlessness caused by attacks that seem unpredictable and unavoidable.

To identify long-delay triggers in a population or an individual, a large dataset is needed in order to avoid false positives and negative. For this reason, many clinicians use patient diaries (e.g. in headache diagnosis work) to identify trigger factors. However, such diaries are often very demanding for the patient to keep, e.g. because of imperfect memory, the wide number of possible trigger factors to record, imperfect knowledge about contents of food items, the demands of job and family that can push aside the task of keeping the diary, the long time that the diary must be kept in order to provide enough

data, and more. As a consequence, study diaries tend to focus only on a limited set of possible trigger factors, in order to make it manageable for the patient to keep the diary.

Details about the challenge and its benefits if solved

There is a huge scientific and clinical potential in developing a tool that will make it possible to record a **large number of possible trigger factor**s (perhaps even ones that are not hypothesized *a priori*), **over a long period of time** (months), and in a way that is **practical** and **minimally demanding** of the patient. Such a tool would also be suited for identifying prodromes, i.e. warning signs that an attack or flare-up is imminent. Identifying such warning signs would in turn allow better management of the attack by enabling early treatment or even prevention.

A tool as described above could potentially significantly improve disease management, diagnosis and pathophysiological knowledge - for patients, clinicians and researchers respectively.

Possible approaches to the challenge

The last ten years have seen an exponential increase in the number of available smart devices, self-tracking apps (Endomondo and others) and wearable sensors (commercial such as FitBit or research devices), but so far these technologies have not been successfully implemented in a tool with the capacities listed above. Patient diary apps ("Min Hovedpine" and others) exist but do not overcome the challenges described (though the challenger obviously does not know all such apps, and new alternatives may exist or be in development).

It may also be possible that a very simple technological solution is sufficient if implemented in a novel, creative way that properly takes into account patient psychology and practical usability of the tool.

Information about BalancAir:

BalancAir is a medical technology company which was founded by Troels Johansen in 2009 in order to develop and commercialize the concept of partial rebreathing, i.e. devices that capture part of the expired air for rebreathing, mixed with a controlled amount of atmospheric air, in order to induce a steady state of moderate hypercapnia with normoxia.

From 2009-2016, BalancAir was a spare-time endeavour, focusing on conducting technical tests and small-scale clinical studies on dysfunctional breathing and epilepsy, respectively. In 2015 it had become clear that the partial rebreathing concept had a considerable potential in migraine treatment, which lead to the decision to raise the venture capital that in February 2016 allowed BalancAir to ramp up its activitites, acquire an office in DTU Science Park, and pay salaries to a core team to allow them to focus on setting up a migraine clinical trial and entering the market. This happened in October 2018, when BalancAir launched the *Rehaler* treatment.

Rehaler is a new type of drug-free device for treatment of migraine with aura. It is especially well suited for patients whose aura starts more than 15 minutes before the headache. The device is used by breathing through it for 20 minutes at the beginning of the first aura or other warning symptoms.

Rehaler works through accurately balanced partial rebreathing, yielding an increase of the inspired CO_2 percentage to a stable, adjustable level between 1.5 and 3.5%, while retaining normal arterial oxygen saturation (S_{aO2}), no matter how long the device is used.

CO_2's efficacy in aborting migraine attacks has been known since 1950 but until now no CO_2-delivering device has existed that was at the same time practical, compact and safe.

The Rehaler treatment was from 2016 to 2017 tested in a randomized, controlled, double-blind pilot study that showed significantly higher pain relief and user satisfaction compared with placebo, and no adverse event were seen. On the basis of these positive results and the safety of the device, it has now been CE approved for sale without prescription, and a large clinical study is in preparation that will test the effect on several different types of migraine.

As a drug-free treatment, Rehaler can be used as an add-on to the patient's normal medicine, or as an alternative for patients for whom pharmaceutical treatments are contraindicated, problematic or ineffective.

BalancAir's interest in the challenge:

The Rehaler device works best when used in the early part of migraine attacks. Unfortunately, many patients do not recognize warning symptoms or triggers before late in the attack's evolution, and consequently are not able to treat early. This leads to suboptimal treatment effects compared to the very significant efficacy seen when Rehaler is used in the pre-headache phase of the attack. Consequently a tool such as the one proposed in the challenge would have the potential to increase the number of patients able to derive benefit from the Rehaler treatment.