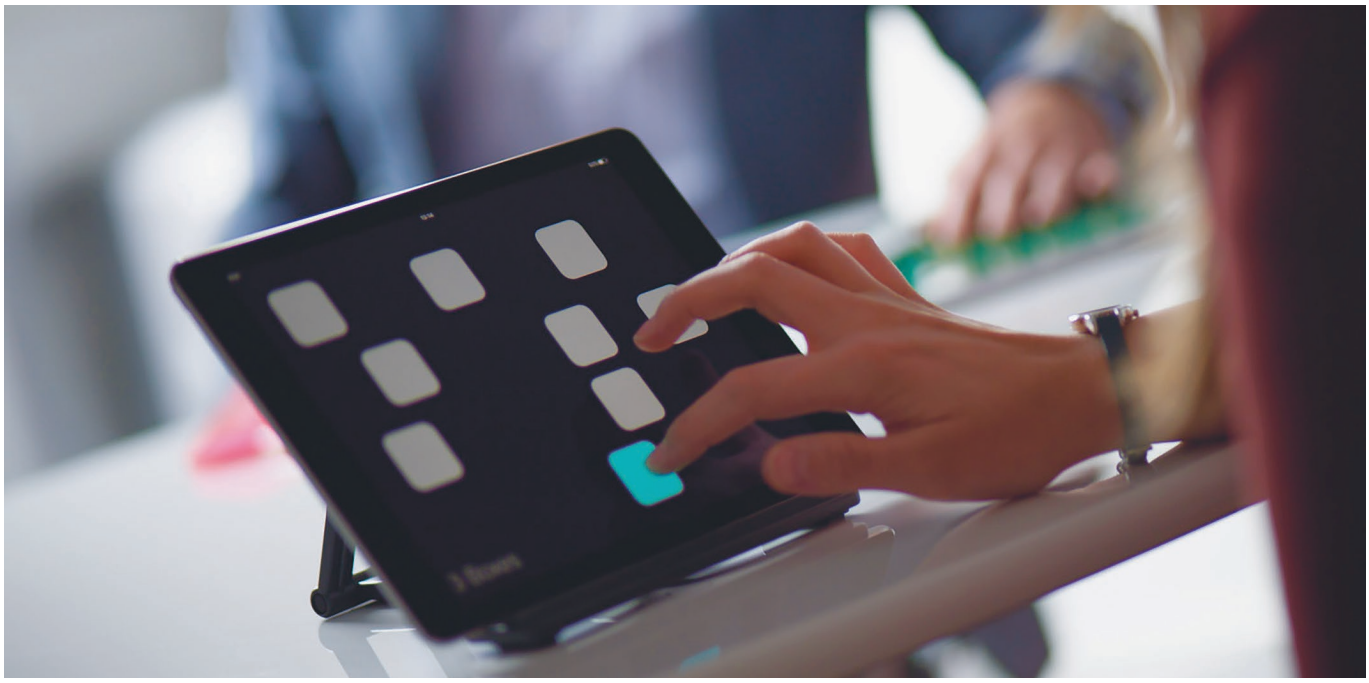
The impact of digital biomarkers and clinical research

By Sheryl Caswell



What are biomarkers?

Biomarkers have become increasingly important in the drug development process. But what is a biomarker and why are they useful to enable clinical trial design?

One definition of a biological marker (biomarker) is that it is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [National Institutes of Health]. Even more simply, a biomarker can be described as a medical sign (rather than symptom, which can be subjective). A useful biomarker needs to be objectively measurable, have good sensitivity and specificity for the process or response that it is predicting or measuring and be shown to be reliable. It is an advantage if the biomarker is technically simple to measure, does not place a large burden on the patient and the test results are available quickly.

Simple biomarkers then do not need to be complicated or only from biological samples. They can include clinical assessments, such as the measurement of blood pressure. Blood pressure is an objective measure of a biological process. It can also be used to assess a response to therapeutic intervention where, for example, medication is taken to reduce hypertension.

Biomarkers in clinical research

Biomarkers can be used for a variety of reasons such as: diagnosis, monitoring the status of a condition, identifying people at higher risk of developing a particular condition and for monitoring patient safety.

However, when the term "biomarker" is used within clinical research it is not generally intended as a direct clinical measure to be used as an endpoint or general diagnosis, but rather as a surrogate marker. This means it can indirectly measure efficacy, indicate a positive response earlier than changes in symptoms would be seen, or stratify a study population to predict those most likely to respond to a specific therapy, such as identifying the presence of HER2 receptors in cancer patients before treating with Herceptin.

Drug development, and clinical research in particular, is expensive and has a high-risk of failure. The use of predictive biomarkers in therapeutic areas such as oncology and cardiovascular conditions, where biological samples can be readily taken and specific biological signatures measured, has improved the likelihood of trial success. The problem of trial failure continues in research for psychiatric and some neurological diseases, with notable failures in the development of therapies for important areas of unmet medical need, such as Alzheimer's disease and dementia, but why is there this difference?

Diagnosis of conditions in psychiatry is complex and based on subjective patient-reports of behaviour and symptoms, including the use of questionnaires. Expecting patients with potential memory problems and mood disorders to report multiple symptoms accurately and objectively is difficult at best. Guidelines for diagnosis provided in the International Classification of Disease published by the WHO and the latest Diagnostic and Statistical

Manual of the American Psychiatric Association both utilise broad lists of symptoms. The combined complexity of multiple symptoms and behaviours and often broad classifications for diagnosis creates biological heterogeneity within the diagnosed patient group. Adding to this already complex picture is the high incidence of comorbidity for psychiatric disease, such as patients who experience both depression and anxiety.

Finding objective and specific biomarkers for psychiatric and some neurological diseases has been difficult. Neither useful stratification nor predictive biomarkers based on biological samples have yet been translated into mainstream research or clinical care, and work continues particularly in the use of "omics" research to identify suitable biomarkers in biological specimens. Use of neuroimaging techniques has identified common structural and functional changes in the brain but these have not yet successfully been shown to be either reliable or able to reliably identify the underlying pathology associated with psychiatric disorders which will respond to treatment. In addition the use of imaging in clinical trials and for patient care is expensive, requires access to limited resource at a hospital or specialist centre and needs expert interpretation.

Digital biomarkers – the new biomarker

There is clearly a need for biomarkers in this therapeutic area and digital biomarkers offer a solution which can be used both in the clinical research setting and for patient care. Digital biomarkers can accurately and reliably measure physiological or behavioural signs using electronic devices such as smartwatches or smartphones. Changes in mood for example may be identified by changes in sleep patterns or duration, and daily activity measured by step count. Periods of anxiety could be identified by changes in heart rate. This data can provide not only objective measures of efficacy, but an indication of clinical meaningfulness.

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Validated tests of cognition are already commonly used as efficacy and safety endpoints across all stages of CNS clinical trials. These tests, which can be delivered to trial participants either at a study site or to devices such as iPads and mobile phones while the trial participant remains at home, require participants to complete tasks rather than report symptoms and provide a reliable and objective measure of function in specific parts of the brain. This inherent specificity has now been used to develop digital biomarkers. From a heterogenous population of patients with a common diagnosis based on symptoms and behaviour a specific underlying pathology can be identified to select for a clinical study those subjects most likely to respond to a specific drug mechanism. The assessments are short, do not often rely on understanding a specific language, and the data are analysed by computer algorithms and made available quickly to clinical site staff.

In addition to the advantages relating to more likely efficacy, precision medicine and stratification can improve the safety of trial participants by identifying subjects who are more at risk of off-target effects and should be excluded; as well as reducing the required sample size in the study and so reducing the number of subjects exposed to a drug in development or potentially having a large group of subjects randomised to placebo.

In summary, a precision medicine approach using digital biomarkers could be used to bring the advantages already seen in other therapeutic areas to clinical trials in the CNS space. Smaller sample sizes at Phase II and Phase III and more focused Phase II clinical trials allows for more cost-effective drug development, reduced likelihood of expensive failure at a late stage and a faster time to market. The eligibility criteria used within the clinical trials will be reflected in the label of a licensed product, but surely a large percentage of a large market is far preferable to high risk of failure at Phase III, large expensive trials and efficacy data diluted by a heterogenous study population.

The increase in stratification strategies and precision medicine in the pipelines of companies with expertise in CNS indications suggests this approach is gaining traction. With the many inherent hurdles in identifying relevant biomarkers from biological samples for CNS conditions and the availability of digital biomarkers, surely it is time for the more widespread use of digital biomarkers in getting the right patient on the right drug at the right time. ■

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Sheryl Caswell, Head of Development, Monument Therapeutics