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Conversation with Bill Byrom & Julian Gillmore: Increasing the Usefulness of COAs in Heart Failure Research

Dr. Bill Byrom, Principal, eCOA Science at Signant Health, recently had the pleasure of sitting down with Professor Julian Gillmore, Professor of Medicine at University College London (UCL) and Honorary Consultant at Royal Free Hospital, and a member of the Signant Health Scientific Advisory Board. They discussed current and future opportunities for increasing the usefulness of clinical outcome assessments (COAs) measures in heart failure clinical trials.

Byrom: Professor Gillmore, it's a real pleasure to be speaking with you today. Please could you first tell me a little about your research interests?

Gillmore: I work at the UCL Centre for Amyloidosis incorporating the NHS National Amyloidosis Centre, which is the sole center in the UK that specializes in this rare condition. I've spent the last 25 years or so doing both clinical and basic science research into this condition. This has included developing novel diagnostic tests with the ultimate aim of early detection of the condition and then improving outcomes for patients.

Byrom: What exciting developments are you seeing coming with regard to new treatments for amyloidosis?

Gillmore: There are a number of developments in the treatment of one particular type of amyloidosis, transthyretin (ATTR) amyloidosis, that commonly affects the heart. This was previously an untreatable and ultimately fatal condition. In the last 5 or 6 years we have seen the development of a number of drugs that we've been involved in testing, and these seem to provide benefit to patients with heart failure as a result of ATTR amyloidosis. Interestingly, it was previously thought to be an extremely rare disease, but because of the new diagnostic techniques that we have developed at UCL, we now know that it is a much more common condition than was previously thought

Byrom: Survival and hospitalization are common primary endpoints in clinical trials in heart failure. The FDA guidance on endpoints in heart failure trials describes the importance of also addressing patients functioning and symptoms and states that "a drug that improves symptoms or function when added to standard of care would be valuable even if it did not improve survival or hospitalization". These are often measured using clinical outcome assessments. In your experience, what are the typical COAs that we see in heart failure clinical trials?

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Gillmore: Many heart failure studies will include some form of quality of life assessment, and typically this will be using the KCCQ (Kansas City Cardiomyopathy Questionnaire) – a disease-specific questionnaire. There are also functional assessments – for example, some trials have used cardiopulmonary exercise testing – but perhaps the most common functional performance test we see is the six-minute walk test (6MWT), which has been used as a functional measure and as a primary or secondary endpoint in many heart failure clinical trials.

Byrom: How responsive is the 6MWT as a measure? It's really a maximal performance test, and a little artificial perhaps in terms of what kind of physical activity patients may elect to do at home – but is it still informative and valuable to measure in this population?

Gillmore: The 6MWT does have limitations. For a start, amyloidosis for example is a multi-system disease affecting elderly individuals and the 6MWT can be affected by many things that are totally unelated to the disease that the drug is trying to treat, so there can be a lot of confounders to account for. On top of that, it's a maximal functional capacity test and it doesn't give any information about when the patient is able to engage with physical activity in real-world situations, away from clinic. However, it is useful as an initial measure of functional status.

Byrom: Given the limitations, are there other measures we should be looking at, in addition to, or as a replacement for, the 6MWT?

Gillmore: We should be looking more at functioning during the course of the day, by using wearables for example. These may be helpful in understanding how much does a patient sleep during the day, how often do they get out of bed, when they do get out of bed how far do they walk? There may also be other patient-reported outcome measures (PROMs) that assess how they are able to conduct activities of daily living and these may be more important to them than how far and how fast they can walk in 6 minutes. So I think there's a lot of room for improvement in assessing meaningful aspects of how patients feel and function by using PROMs and wearables.

Importantly with performance tests like the 6MWT, we rarely measure how patients feel when they are undertaking them, or when they are going about their normal activities at home. So, the combination of an objective measure such as steps per day or distance walked in 6 minutes is important to combine with an understanding of how the patient feels, and their perceptions about their activity.

Byrom: Maybe one final thing to touch on, we hear a lot about decentralized trials across the industry. In the types of patients you see is there an opportunity to conduct certain trial elements remotely, or measure more things in the home environment, and would that be beneficial to patients?

Gillmore: There's a huge role for decentralized trials in the disease I specialize in, but also more generally in rare diseases. Rare diseases are often associated with specialist centers, and there may

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be only one center in a country, as in the case of the National Amyloidosis Centre, or several regional centers. In both cases it can be very challenging for patients to get to these centers, and particularly to attend regularly during a clinical trial. Being able to decentralize, and measure things more locally, may really improve the practicality of participating for the patient. There are many things that can likely be measured equally accurately locally compared to at the specialist center. However, many patients with rare diseases do value being able to see their specialist physician from time to time. My understanding is that decentralized in Signant's perspective means a mixed model of some central assessments and some assessments closer to home, and in my view that is absolutely the model that (a) will provide accurate data, and (b) will suit patients and improve patient retention.

Byrom: Thank you, Julian, that was really interesting and insightful.

Julian Gillmore gained his medical degree at University of London. He trained in nephrology and undertook MD and PhD degrees in the field of amyloidosis. His research interests include pathogenesis, diagnosis and treatment of amyloidosis.

Dr. Byrom has worked in the pharmaceutical industry for 30 years. He has authored over 70 publications and two industry textbooks on electronic patient-reported outcomes (ePRO). His recent scientific work includes the use of wearable technology and bring-your-own-device (BYOD) eCOA in clinical trials

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