ECNP Experimental Medicine Network

Agenda and Minutes

Validating new biomarkers for unmet needs in the management and treatment of depression

7-8 February 2023

Meeting Agenda

Chairs: **Gerry Dawson, Dennis Hernaus and Andres Reif.**

Session 1

2.00 pm	**1. Introduction and welcome**	***Chair: Andreas Reif***
	a. Overview of objectives for meeting	**Gerry Dawson**
	b. Optimising the treatment pathway for rapid-acting antidepressant (RAAD)	**Gerry Dawson**
	c. Developing biomarkers sensitive to the therapeutic effects of non-reuptake blocking antidepressants	**Dennis Hernaus**
2.30 pm	**2. Clinical trials and the current state of the art**	***Chair: Gerry Dawson***
	a. Active and planned clinical trials with RAAD's	**Peter Schueler**
	b. The role of biomarkers and study designs in clinical development of RAADs: State of the art and future directions"	**Daniel Umbricht**
	c. A GPS for finding Biomarkers for Relapse in Treatment-Resistant Depression	**Caroline Golden**

3.45 pm	**Break**	
4.00 pm	**3. Potential biomarkers to monitor response and relapse following treatment with RAADs** a. Using FERT to monitor response and relapse following treatment with esketamine b. Monitoring response and relapse with BeHapp c. Genetic variants associated with antidepressant response – potential for stratification? d. A single platform for real-world measurement functional neurophysiology for drug engagement, and therapeutic effects	***Chair: Dennis Hernaus*** **Andreas Reif** **Martien Kas** **Ole Andreassen** **Brain Murphy**
5.45 PM	**Discussion**	
	Session 2	***Chair: Andreas Reif***
9.00 am	**4. Developing biomarkers sensitive to the therapeutic effects of non-reuptake blocking antidepressants** a. Non-reuptake blocking antidepressants – what markers should we look for, and in which populations? b. Getting pharmacological with MRI c. Autonomic nervous system activity as a biomarker for depression	**Dennis Hernaus** **Mitul Mehta** **Stephan Claes**

10.30	**Coffee break**	
11.00	**Discussion and path forward**	
1.00 PM	**Lunch**	

Meeting Minutes

Session 1

Introduction and welcome

Chair: Andreas Reif

Overview of objectives for meeting and optimising the treatment pathway for rapid-acting antidepressant (RAAD) - Gerry Dawson

Gerry Dawson (GD) provided an overview of the meeting objectives, which were to explore biomarkers to optimise the treatment pathway for RAADs and those sensitive to the therapeutic effects of novel non-conventional (i.e., non-5-HT [reuptake inhibition]) antidepressants. In addition, the meeting sought to determine whether there was interest in forming an academic-industry partnership to evaluate and validate biomarkers of interest. GD highlighted the need for biomarkers for relapse following treatment with RAADs. Response to RAAD's is readily detected however, detecting relapse is more difficult as patients relapse at different, and currently unpredictable, rates. Thus, most patients treated with RAADs may require a personalised treatment approach.

Nic van der Wee (NdW) also provided a summary of the ECNP networks. The ECNP networks aim to foster translational research, and support collaborations in and outside of ECNP. The current networks form a matrix of disease orientated and transnosological groups. The disease orientated networks promote the study of specific disorders of the brain, to support research into diagnosis and treatment in patients. The transnosological networks are more focussed towards themes and methodologies.

Developing biomarkers sensitive to the therapeutic effects of emerging antidepressants – Dennis Hernaus

Dennis Hernaus (DH) presented the case for biomarkers that are sensitive to the therapeutic effects of emerging antidepressants with non-conventional mechanisms of action (MoA). For example, pharmacological agents that do not primarily act as SSRIs are increasingly being considered as compounds with antidepressant properties (e.g., kappa-opioid receptor (KOR) antagonists; GABA positive allosteric modulators/neurosteroids; ketamine). The unique MOAs of these agents offers new ways to counteract anhedonia and low mood. Importantly, however, these novel antidepressants may act on neural/psychological mechanisms that differ from SSRIs. For example, some of these agents (e.g., KORs) may exert effects on negative valence, stress, or regulatory systems, for which biomarkers may be currently lacking. Capitalizing on the opportunities will thus require the development of robust endpoints that are sensitive to the unique effects of these agents.

Clinical trials and the current state of the art

Chair: Gerry Dawson

Active and planned clinical trials with RAAD's - Peter Schueler

Peter Schuler (PS) provided an update on current active and planned clinical trials with RAADs. A targeted search of Trialtrove revealed 877 depression trials, however only 1.3% included the words rapid and fast, suggesting very few ongoing trials with RAADs (although it should be noted that there be many more trials of this type they may not be identified by these key words). Of those 11 ongoing trials, the majority, involved esketamine, with most of trials being conducted in academia. Pharma involvement in trials is higher in trials that include the terms TRD and suicidal ideation, most of which investigated ketamine and psilocybin. Other treatment mechanisms are emerging, for example drugs targeting the orexin system, muscarinic receptor, PDE4 inhibitors, and MDMA are re-emerging for several indications, thus increasing the demand for relevant biomarkers.

The most common clinical outcomes are still treatment-induced changes in MADRS and HAM-D scores and it is clear that new validated endpoints and biomarkers are needed to progress the field.

The rapid development of COVID-19 vaccines are a key example of how the approval for the regulatory requirements for clinical trials can be accelerated when required. It remains to be seen if this accelerated approval process can be applied to other clinical indications, particularly for brain disorders where clinical development timelines are often challenging. The lack of validated biomarkers that can predict early and long-term treatment effects has resulted in clinical trials with extended treatment periods to determine efficacy and relapse prevention. As a result of among others attrition, these clinical

trials also require large sample sizes to assess treatment efficacy. Phase II and Phase III trials rely on traditional questionnaire or interview-based endpoints (e.g., MADRS, HAM-D) where change from baseline is the usual outcome measure. Clearly these endpoints are not appropriate as an indicator of efficacy in healthy volunteer Phase 1 trials. PS mentioned that one reason for the reliance on such endpoints is that regulators favour endpoints that represent a direct benefit for the patient, for example a reduction in reported symptoms and improved wellbeing. Thus, ideally, newly developed biomarkers would need to be associated with outcomes measures that patients themselves perceive as being relevant to their health. As such, patient involvement is key during the development of biomarkers and patients' feedback should be sought as early as possible, and shared with regulators. At the same time, however, it was also noted that such biomarkers may be of less benefit to researchers, as biomarkers that provide direct patient benefit may not inform the mechanism of action of treatment. In addition, there may be interindividual differences in the positive treatment outcomes that patients may value, which may result in analysis-related/statistical challenges.

b. The role of biomarkers and study designs in clinical development of RAADs: State of the art and future directions – Daniel Umbricht

Daniel Umbricht (DU) outlined how a biomarker can be defined as any data manifesting pharmacological, biological, physiological, and behavioural processes that are not directly observable in signs and symptoms. DU discussed how the role and nature of biomarkers changes during the various stages of drug development. During phase 0 and phase 1 target engagement is critical. During phase 1b, biomarkers should be able to detect biologically and clinically relevant drug-induced effects. In phase II, biomarkers should support diagnosis and likelihood of response. Phase III biomarkers should capture the course of remission and relapse. From an industry perspective, the key aspects to consider when developing news biomarkers is:

- Ease of implementation
    - For example, imaging is useful for determining circuit engagement but is difficult to implement in large cohorts, while smartphone biomarkers are much easier to implement across large groups but provide little information about circuit engagement
- the burden placed on patients
- translational from animals and humans and back again
- the association they have to the patient phenotype.
- Replicability
    - The test-retest reliability is not known for many biomarkers. If biomarkers are to be useful for decision making it is critical to determine how well they are measuring what they are meant to measure.

Lack of target engagement is an important consideration during biomarker development as a third of trials fail because of it. Biomarkers that confirm target engagement are valuable even in the absence of clinical effects, because they ensure appropriate dosing and demonstrate that the lack of clinical effects is likely due to a lack of efficacy. It was noted that reward functioning and emotion processing biomarkers are useful, but that such phenotypic assessments cannot assess the pharmacology of the disorder of interest.

Commonly, the lack of validation and unknown reliability of many biomarkers means that they cannot be used to support go/no-go decisions at critical stages of drug development. However, reliable biomarkers to assist go/no go decisions in early development are crucial for small biotechs who do not have the funds to conduct large efficacy studies. It was noted that the Alto Neurosciences open-label study with ALTO-100 showed that the probability of success may be increased if the patient population is defined by an EEG biomarker that predicts an early treatment response. However, this approach increases development timelines and ultimately reduces market size to biomarker-sensitive patients. A discussion on stratifying patient populations, and the reduced market size that follows from it, concluded that this will inevitably lead to a higher price for drugs given the high cost of development. Careful labelling and diagnosis also need to be considered. For example, clinicians may need a specific diagnostic biomarker for a drug that is labelled for the treatment of anhedonia alone.

c. A GPS for finding Biomarkers for Relapse in Treatment-Resistant Depression – Caroline Golden (Compass Pathways)

Caroline Golden (CG) gave an overview of COMPASS's approach to developing biomarkers for relapse following treatment with psilocybin. One third of depression patients who reach remission will relapse, therefore the aim for a successful treatment is to prevent relapse, which requires biomarkers that predict relapse. The current best prediction methods are self-report questionnaires; however, these are reliant on patient compliance and often need to be confirmed by clinical interview.

COMPASS have considered two frameworks to assess biomarkers for relapse prevention:

1. **Bottom-up approach.** This approach is driven by the mechanism of action, making it more scientifically robust.
2. **Top-down approach.** This relies on careful observation of clinical outcomes, and is generally more pragmatic.

Although both approaches are important there is often a clash between them.

It is important to note that biomarkers are distinct from symptoms, and that there are there are many types of biomarkers including:

– Primary biomarkers

- Secondary biomarkers - based on downstream consequences,
- Static biomarker - apparent at discrete time points
- Dynamic biomarkers – become apparent over time.

It was noted that there is often a trade-off between real-world feasibility and clinical feasibility. COMPASS is aiming for passively monitored biomarkers with strong scientific validity in an identified patient cohort. As such, they are favouring a top-down approach, but it would also be useful if the biomarker was linked to the antidepressant mechanism of action (MoA) of psilocybin.

Recently there has been some promising progress in biomarker research. Technological advances offer more opportunities: increased EEG feasibility, research into natural language processing, and increased MoA research are all promising approaches, however, each has unique challenges. Integrating multiple biomarkers may be needed for reliability and it is critical that biomarkers are tested on independent datasets to ensure validity. Replication is a key issue and it would be useful to have consistent measures across all studies.

It was noted that the top-down approach is reductionist, as diagnosis is often underpinned by vastly different MoAs. Although the phenotype is the same, it may not reflect the underlying biology, therefore a pragmatic approach may be needed.

Potential biomarkers to monitor response and relapse following treatment with RAADs

Chair: Dennis Hernaus

Using FERT to monitor response and relapse following treatment with esketamine - Andreas Reif

Andreas Reif (AR) gave an overview of esketamine treatment in depression. The main issues with ketamine treatments are unpredictable relapse and knowing when to re-dose. The dosing regimen for Spravato is flexible, however there is a clear need for biomarkers to determine when and whether to re-dose.

AR described a pilot study in which TRD patients were treated with IV esketamine. The FERT, FeelZoom and MoodZoom data were collected immediately pre-infusion and 4 hours post-infusion. The FERT post treatment data showed reduced accuracy for recognising sadness at low intensities and a lower misclassification rate for sadness, suggesting reduced negative emotional bias. There was also an increase in fear accuracy, perhaps due to increased alertness or cognitive ability. Interestingly, repeated infusions were needed provide a sustained reduction in negative emotional bias. In addition, the FERT results correlated well with the MoodZoom, FeelZoom data and improved cognition. These data suggest that multiple infusions of esketamine are needed to achieve a cumulative and sustained effect on negative bias and potentially depressive symptoms.

The TRD population seem to be very sensitive to sad faces, while patients who respond to SSRIs appear to be more sensitive to fearful facial expressions. Thus, sensitivity to sadness seems to be less prevalent in the healthy controls and non-TRD population. SSRIs exert a general emotional blunting affect, whereas psychedelics appear to have an energising affect and it may be interesting to explore these differences using the FERT.

Questions about learning effects and the lack of a placebo group in these studies were raised. There was no placebo group in this study, but rather treatment as usual, which can be used as a control. To overcome learning effects on the FERT, different actors are used as this reduces habituation to specific emotions. In addition, the intensity of faces is balanced to ensure that the accuracy of identifying an emotion is similar for all emotions.

Monitoring response and relapse with BeHapp – Martien Kas

Martien Kas described how digital phenotyping is unobtrusive, more objective, occurs in real time and provides real world quantitative outcomes. He presented data from the PRISM project showing that there is often a deviation between the patient and researcher, or companion, on questionnaire measures. For example, patients tend to overestimate their social interactions compared to their carers. Assessments of drug effect may therefore differ depending on who is asked, the patient, carer or clinician.

BeHapp remotely monitors social behaviour and is GDPR compliant. The app records multiple measures such as the number of steps, outgoing and incoming calls, and GPS data (i.e., time spent at home, variety of areas visited et.). Research has shown that BeHapp can differentiate between SZ and HC status. In addition, data from BeHapp showed that MCI participants had reduced social contacts and variety of locations visited compared to controls. BeHapp longitudinal assessments can also identify changes in human behaviour such as reduced movement as a result of COVID-19 lockdown. Continuous monitoring may help detect and respond to relapse following treatment with RAADs.

An ongoing study (SMARD) is aiming to improve the detection of early symptoms of recurrent episodes of depression, and to develop cognitive training to prevent relapse. Data will be collected over an 80-week period, with the aim of creating an relapse-prediction algorithm based on a variety of clinical measures. BeHapp is easy to implement, provides high resolution, longitudinal, and passive data collection.

During the discussion, questions were raised about whether the BeHapp algorithm needs a training period for each patient, or whether the algorithm is a generalisable from patient to patient. The aim is to have a generalisable algorithm. Also, it was discussed whether the app can capture different usage types of phones, i.e., work related or personal calls. In order to increase the validity of the app, it will be necessary to align the data with psychopathological symptoms and connect these phenotypes to the

biological symptoms. Interest in correlating BeHapp data with clinical symptoms and real world stress was expressed. In addition, monitoring circadian rhythms and sleep patterns in patients with depression may shed light on mechanism of response and relapse.

Genetic variants associated with antidepressant response – potential for stratification? – Ole Andreassen and Kevin O'Connell

Using large samples of genotyped patients, genetic variants associated with antidepressant response have been identified. In addition, pharmacogenetics can allow us to uncover genes with adverse effects.

The presentation focussed on patients responding to SSRIs, due to the availability of data. Genetic correlations are associated with SSRI response and non-response has been shown to negatively correlate with high blood pressure and coronary heart disease. It was suggested that polygenic signals may help prediction of SSRI response and the number of antidepressants used, which opens the potential for genetic stratification. However, there is a still a long way to go before these observations could be used in clinical practice. There was also discussion about how big these effects need to be to influence clinical practice. It was noted that it is unlikely that genetics will be used alone, but rather in combination with other measures. In addition, in the absence of alternative treatments the ethics of being able to predict non-response well to an antidepressant was raised and whether biomarkers could be validated.

A single platform for real-world measurement functional neurophysiology for drug engagement, and therapeutic effects – Brian Murphy

Brian Murphy described how EEG measures may be of useful for research on depression. Functional recordings can objectively measure cognition, sleep, neural mechanisms (e.g., neuroplasticity), as well as target engagement of specific drugs. EEG can enable the objective measurement all of these aspects whilst remaining scalable. Measuring EEG recordings at scale, and frequently, gives aggregate measures which may be more reliable. Frequent measurements can reveal longitudinal trends with greater sensitively.

The Cumulus platform is located on a restricted tablet and includes a battery of established tasks, including cognition, EEG, mood tasks, and language tasks. Development of this platform has incorporated patient feedback to ensure it is suitable for all groups, i.e., schizophrenia patients do not like the words ‘monitor’ or ‘track’, therefore these words have been removed when used this group. The Cumulus EEG headset can be worn while completing the battery of tasks, with high time precision. After completion, sessions are automatically uploaded to the Cumulus platform and can be viewed by the clinician. The headsets can be used both in the clinic and at home, and are currently being used in phase 1 and phase 2 studies, with 70-80% adherence. Studies are currently ongoing in Dementia, ALS, FTD, and HCs.

It was questioned how much dry home EEG data are needed to get the same quality as data obtained in the clinic. In general, 2-5 at home sessions have the same level of noise as a single in-clinic session. Thus, a single home session is not as reliable as a single supervised clinical session, but repeated sessions at home can have the same, if not better, quality than a single clinical session.

The visual evoked potential task (VEP) is a non-invasive measure of LTP and can directly measure neuroplasticity in around 10 mins. Research shows healthy controls exhibit plastic modulation of VEP. The Cumulus platform can also measure atypical responses to emotional faces via the N170 response.

It was discussed whether all studies could use the same tasks. For each study, Cumulus could do a task selection for each sponsor. Experience has shown 2+ EEG measures plus behavioural data over multiple days increases the accuracy of the data.

There were also questions on data monitoring and whether there is technical support if people cannot use the technology. The Cumulus teams train site staff, and also provide second level support. In addition, the Cumulus dashboard generates alerts to identify any issues as they arise.

Developing biomarkers sensitive to the therapeutic effects of non-reuptake blocking antidepressants

Chair: Andreas Reif

Non-reuptake blocking antidepressants – what markers should we look for, and in which populations? – Dennis Hernaus

Dennis Hernaus (DH) described how non-SSRIs may exert antidepressant effects that occur beyond/outside of the serotonin system. For example, agents like aticaprant and ketamine have affinity for opioid receptors. Although this is not the primary MoA of ketamine, this affinity is noteworthy, because these receptors are distributed throughout the brain, including on reward/motivation systems. In the example of opioidergic agents, complementary non-SSRI antidepressant effects may also occur via negative valence (e.g., fear, anxiety), regulatory (e.g., sleep, arousal), or stress systems, pointing towards potential state-dependent antidepressant effects. However, the problems of probing the MoAs of these systems are complex. Developing biomarkers for stress/inflammatory responses may be informative of these mechanisms, and can be collected in either a clinic or real-world setting. To assess the state sensitivity of commonly-used markers, it may also be useful to study how such endpoints (e.g., motivation/effort/reward decision making) are sensitive to changes in stress states. Preliminary data presented by DH shows that (effort-based) reward motivation is in fact not sensitive to stress states, but avoidance motivation (effort to avoid punishment) may be. Endpoints that have good test-retest reliability, but also sensitive to state effects, may yield insights to the MoA of non-SSRIs.

Discussion was focussed on whether direct comparisons of SSRI/non-SSRIs would be useful and the need for robust endpoints in such comparisons. In addition, the difficulties in calibrating common inputs for experimental endpoints (e.g., shock threshold, grip force) were discussed. Some of these difficulties can be avoided by re-calibrating on every session. Recent work has also started to look at test-retest reliability of these variables (e.g., RTOC). Some guideline papers have already been released. Discussion also touched upon the lack of good (lab-based) reward tasks. Here, ambulatory measures in combination with reward tasks would provide some benefit. The heterogeneity of samples in studies due to inclusion based on DSM criteria (and no neurobiological information) was also discussed.

Getting pharmacological with MRI – Mitul Mehta

Mitul Mehta (MM) described how we can obtain better, more mechanistic, information from MRI. There are currently many MRI techniques, however not all of these are direct measures of brain systems that are modulated by drugs. Using and interpreting fMRI data has many challenges including neurovascular coupling, temporal and spatial resolution, and movement.

MM addressed how haemodynamic activity reflects underlying pharmacological information. MRI has no intrinsic selectivity for activity at receptor sites. For some drugs it is possible to track their

pharmacokinetics through this measure and then correlate with brain areas that show the same temporal profile. This works well for some compounds, such as nicotine, but not for others, such as glucocorticoids. Receptor blocking studies translate well from rodents to humans and coadministration of drugs have provided useful in investigating the pharmacology of NMDAR receptors. However, this approached is limited by the availability of agonists and antagonists at the same receptor (and subtypes) and the side effects they induce.

MM also discussed receptor occupancy theory. Change of blood flow correlates well with receptor occupancy, and some of the variance in change of blood flow can be attributed to action at receptors. One promising way to gain more mechanistic insights into the neural effects of drugs is to supplement MRI data with information about local expression of receptors (e.g., based on PET or post-mortem studies). This technique, developed in MM's group (see REACT; https://pubmed.ncbi.nlm.nih.gov/30953835/), can reveal if indeed drug effects occur in brain regions that also exhibit expression of receptors that have affinity for the agent. The correlation of MRI measures and behavioural outcomes was also discussed and the lack of fMRI dose response studies was highlighted although observing dose related changes has been possible in some studies.

Autonomic nervous system activity as a biomarker for depression – Stephan Claes

Stephan Claes described research on stress as a risk factor for psychopathology. He noted that it is possible to assess the stress response via cortisol, ACTH, and CRH. It is also possible to assess autonomic nervous system activation through monitoring heart rate (HR), heart rate variability (HRv), and breathing rate. Wearables have provided assessments of stress variables that can be studied in the laboratory and in the real world.

There is a strong relationship between physiological stress measures and reports of subjective stress. Some people are very good at identifying when they are stressed, while others are not. People with few high stress moments show a clear correlation with subjective stress and arousal – possibly indicating a healthy stress system. In contrast, people with chronic stress have more depressive symptoms and poor sleep, potentially indicating an unhealthy stress system. When assessing stress physiology in depressed patients it was observed that the recovery from stress is not as fast as in healthy controls. Moreover, the stress recovery of depressed patients (i.e., the decline in stress variables over time) takes longer and does not always fully go back baseline levels. In addition, physiologically, HR does not follow the same pattern and does not react to a second stressor, perhaps indicating an exhausted physiological response. Other research has shown that MDD patients have higher HR diurnal patterns. However, there is a need for long term studies to replicate and validate these findings. This should be feasible as HR and skin conductance can be readily and reliably measured with wearable devices. There is potential for this research to be used as an early warning sign of impending relapse or possibly therapeutic efficacy.

There was some discussion regarding Experience Sampling Method (ESM), and how this might miss important events as these are momentary in nature. It was suggested that peaks in HR can trigger the prompt to complete subjective stress measures, but this needs to be further researched to confirm this finding. More research is needed to determine whether depression is characterised by high peaks, or rather more by irregular day-night patterns and flexibility of symptoms. There is also some uncertainty about whether changes in stress-variables should be viewed as a trait/vulnerability marker, or a state marker.

The question of physical fitness of patients with depression arose as they are usually less fit than health controls and that it needs to be considered during study design. Measures of skin conductance are affected significantly by environmental factors and therefore may be more difficult to measure reliably than suggested. Similarly, sex differences have also been noted for these measures they are influenced by the menstrual cycle. It was noted that monitoring stress related measures may be of great value if it can predict or enable the diagnosis of the depression.

CONCLUDING DISCUSSION:

The question of what we mean by biomarkers and whether different biomarkers are required at various stages of development was raised throughout the meeting. It also became clear that biomarkers are needed for patient stratification for clinical trials and to monitor early response and relapse in clinical and real-world settings. It was noted that the reliability of biomarkers was dependent on patient adherence to treatment and to requests to provide measurements or answer questionnaires. Clinical trial and treatment outcomes are still reliant on scales developed decades ago and new treatments require more sophisticated and specific biomarkers. However, it was noted that, in some cases, it has been shown that questionnaires are more sensitive to clinical changes than more recently developed tasks based on psychological concepts. This raises questions about the robustness of these latter endpoints.

It is clear that real-world measures of patient outcomes are important not just to patients but are also important for regulatory boards. As such, it is important to gain patient input in the development of new biomarkers and outcome measures. To this point, in a recent study of depressed patients (https://pubmed.ncbi.nlm.nih.gov/33637837/), patients optionally chose to continue their treatment using the QIDS to monitor their symptoms, as they found it informative and beneficial regarding their treatment and progress. In addition, these data enabled GPs to determine whether patients were responding to treatment or relapsing. A key question to address is whether patient monitoring of symptoms can help patients better understand their symptoms and provide more granular feedback. For example, if an improvement in detecting symptoms of anhedonia is achieved, are patients aware of and benefit from

this improvement? Thus, biomarkers that capture, or are closely related to, patient-reported improvements in quality of life will be beneficial when discussing clinical results with regulators.

As the specificity of drug treatment for particular symptoms increases there is a clear need for biomarkers that both stratify patients for clinical trials and treatment. For example, a clinical trial in depression with the anti-inflammatory drug infliximab was negative, due to the fact that it did not stratify for the presence of an inflammatory signature (https://pubmed.ncbi.nlm.nih.gov/22945416/). Post-hoc analyses however demonstrated an effect in patients with elevated baseline hsCRP, arguing for the necessity to incorporate predictive biomarkers in studies targeting specific mechanisms.

The meeting closed with an agreement that further work will be needed and that the next meeting of the group would focus on defining those biomarkers most urgently need to develop emerging drug treatments. In this meeting, the perspective of industry, as well as, ideally, regulators, will receive more attention.