Conclusions of the RSNN Expert Meeting entitled 'Precision Medicine for Chronic Diseases Using Biomarkers: Diabetic Nephropathy as a Case Study' held on 18 February 2020

The RSNN Expert Meeting of 18 February 2020 discussed and elaborated potential research questions on the theme of 'Precision Medicine for Chronic Diseases' using diabetic nephropathy as a case. Fifteen experts and stakeholders were invited in a personal capacity to discuss this theme. The participants have knowledge and experience of the theme through their specific work experience in government, industry and/or universities. A patient representative joined the meeting to bring a patient's perspective to the discussion. The meeting was held under the Chatham House Rule. This report contains a brief summary of the meeting, divided into sub-themes, including the most relevant regulatory science research questions for the RSNN's knowledge agenda, also described per sub-theme.

1. PROBLEMS WITH CURRENT MEDICINE RESEARCH

Clinical trials for diseases such as diabetic nephropathy, but also cardiovascular and metabolic disorders, often strand in phase III after initially promising results in phase II trials, whereby the medicine proves to be ineffective or even harmful in the target population. The main reasons for this are (1) patients react very differently to therapies and (2) the populations tested in phase III trials are more heterogeneous and less controlled than in early clinical trials, resulting in an even greater variation in the response to the tested medicines.

Often, subgroups can be identified in these heterogeneous populations that do respond well to the therapy, while in other subgroups the medicine is ineffective or possibly even harmful. Regulators have recognised this issue and advocate well-designed follow-up trials of these subgroups to demonstrate the effectiveness of a medicine. However, the investments involved must be weighed against the returns.

Research questions:

- Which clinical trials failed in phase III due to the patient selection method used and can we identify areas for improvement in the stratification of the population?
- How can the results of failed major trials be reused to develop a successful medicine for the target population? Should developers be encouraged to continue the development of these medicines?
- Clinical trials are conducted at the population level, while precision medicine focuses on treating individuals. How can we adapt clinical trials to match the natural variation in the patient population?
- What do clinical practitioners do when there is a lack of an effect on a particular endpoint? Are studies conducted on this after therapy? If so, what is the consequence for the follow-up therapy? Is a combination therapy applied?

2. BIOMARKER DEVELOPMENT, VALIDATION AND QUALIFICATION

The idea behind precision medicine is that clinical trials can be designed more efficiently, with better patient selection methods leading to more patients that respond well to the medicine and that experience fewer side effects. This can be achieved, among other things, by measuring biomarkers ('enrichment') in the clinical trial. Three situations in which biomarkers can be used were discussed during this Expert Meeting: (1) biomarkers that can identify patients with an increased risk of reaching the clinical endpoint, (2) biomarkers that can identify patients who respond better to the therapy, and (3) biomarkers that can predict the long-term response based on the short-term effect of a medicine. The problem with using and assessing biomarkers is that it is difficult to determine what the exact threshold values should be (upper/lower threshold vs. 'normal'). Moreover, it is often unclear what the optimal frequency and duration of the measurements should be. Some biomarkers, such as albuminuria, have high interindividual and intraindividual variability (this is particularly the case in systemic diseases). This could be resolved by conducting repeated or continuous biomarker measurements. In addition, the trials often focus too much on a single target biomarker, so that certain side effects of the medicine which could be reflected in other biomarkers are not measured. The measurement of these potential drug effects should be considered at an early stage of the study design so that they can be included in the post-hoc analyses. A biomarker 'panel' such as the PRE score could overcome this problem. The validation and qualification of biomarkers or biomarker panels could lead to generalisable endpoints with sufficient sensitivity. However, at present only a small number of biomarkers are qualified for use in clinical trials. It is unclear who should be the initiators of the development and qualification of new biomarkers. University research groups are often the driving force behind the development of potentially relevant biomarkers, but these often lack

the resources needed to get a biomarker through the official approval procedure. In comparison with medicines, only a very few biomarkers are actually registered on the basis of only scientific research. More effective cooperation between the scientific community, the industry and regulators could help to optimise this process. It is important to differentiate between using a biomarker (or biomarker panel) to register a new product and using it to optimise an already existing therapy. In the latter case, the research question often includes comparisons between various therapeutic scenarios.

Research questions:

- Which factors lead to successful biomarker qualification? How have the guidelines for biomarkers and their application been formulated in recent studies? Should these guidelines be interpreted narrowly or broadly? Would it be useful to draw up new guidelines?
- Why are some developers not interested in getting their biomarkers qualified? Which developers does this mostly apply to? How can it be made more attractive for them to get their biomarkers qualified?
- To what extent are clinical trial results based on qualified biomarkers interchangeable? Does this only apply to a single, specific test method (‘companion diagnostics’)? To what extent should the test method also be validated?
- What could lead to the discovery of new biomarkers and who should initiate this discovery? Will this require cooperation between science and industry (for example)?
- What are the critical points in the biomarker life cycle for effective development and how can this process be optimised?
- Should there be more focus on genetic markers in the stratification of patients in clinical trials? (Genetic markers are less affected by fluctuations and have been much studied and successfully implemented in oncology.)
- Taking into account the complexity of chronic diseases and the possibility that several biomarkers play a role in the effect of a treatment, could a biomarker panel be used and validated to generate a patient profile? Will this make the stratification of patient groups and/or measuring the effect of a treatment more or less reliable? Is it also possible to have a panel of biomarkers validated and qualified? How do regulators respond to this?

3. INTERACTION WITH REGULATORS

New clinical trials are usually designed using methods and/or endpoints that have been used in previous trials. The patient population is also often selected on the basis of existing data. New study designs, analyses and selection methods are seldom used because the consequences are unknown. The use of new biomarkers is also met with hesitation, particularly in the industry, where deviating from existing guidelines entails too great a risk of

rejection by the regulators. The guidelines drawn up by regulators describe validated endpoints and methodologies for medicine research in each separate category of diseases. Regulators report that requests for advice on the design of phase III clinical trials mainly concern the question of whether or not the study complies with these guidelines. The innovative designs often described in the literature, such as 'platform', 'bucket' and 'umbrella' trials, do not feature prominently in the requests for advice. However, regulators do say they are open to an early dialogue, innovative ideas and scientific discussions in which the best approach to a new trial can be discussed. Interacting with involved parties at an early stage to fine tune methods and the choice of study population can also provide important benefits in terms of drug reimbursement (if HTAs are involved).

Research questions:

- Can the number of successful phase III trials be increased if:
    - Pharmacists seek scientific advice from regulators at a different/later moment, i.e. when more information is available on the results/mechanisms of phase II?
    - Pharmacists are more open-minded in their requests for scientific advice from regulators, so that they can discuss the design together rather than only submitting yes/no questions about compliance with the guidelines?
- Could workshops on the design of clinical trials for particular categories of diseases, attended by regulators and various developers, help to remove the aforementioned hesitancy to develop new biomarkers? If so, how can we foster the confidence required to temporarily put aside the interests of all the stakeholders?
- Do overly specific guidelines and previously validated endpoints prevent innovation with regard to the use of new biomarkers in the design of new clinical trials?
- What is the right balance between innovation and successful development from phase I to phase II trials? Should we implement standard procedures to get medicines to market as quickly as possible? Or should we put innovation first, with the risk that this will take longer, but with the advantage of successfully completing more phase II and phase III trials?
- Can platform trials offer a solution when a specific active compound is not yet in the picture? (Because developers will then be more inclined to broaden their search for innovative solutions.)
- Could HTAs be included earlier in the drug development cycle, i.e. as part of the interactions involved in the design of new clinical trials? How could this be achieved?

4. REGISTRIES, DIGITAL HEALTH AND MACHINE LEARNING

For precision medicine to be a success, it is important to improve our understanding of disease progression and heterogeneity between patients to improve the chances of new

medicines being authorised. Disease registries, with their wealth of disease information, could help to achieve this. They allow us to search for the most important variables for predicting disease progression, possibly in combination with tools such as machine learning. The results of these searches can then be used to select the most suitable patients for a trial. However, establishing, linking and maintaining registries runs up against issues with privacy and other legislation (particularly in Europe) and finding long-term funding. Moreover, patients may take issue with their data being collected and used (although they may well be fine with this if there is a clear policy and their wishes and opinions are listened to). Another possible source of relevant data are wearables such as smartwatches or apps on mobile phones (these should be CE-certified). These devices can be used to collect 'digital biomarkers' that can provide continuous insight into the progression of certain diseases. Moreover, these technologies can also help to improve therapy adherence, for example with the use of reminders or alarms. Nevertheless, there are still various shortcomings and unanswered questions related to these technologies.

Research questions:

- It is difficult to control the conditions under which registry data are collected. For example, you cannot retrieve information about matters that are not in the registry, such as whether the person in question has just eaten or not, while such variables may be included in a trial. Does this lead to problems? How good is the quality of registry data?
- Can machine learning provide us with more information about complex conditions and thus lead to more targeted clinical trials? Do regulators accept the information provided by complex algorithms as a form of scientific evidence in clinical trials?
- Can digital markers and wearables be used in clinical trials? Can the information they generate be assessed by regulators?
- How can we resolve existing problems with registries, and especially privacy?

The RSNN will incorporate the results of this meeting in future research agendas to inform policy discussions at the interface between regulation, science and industry.