NEWSLETTER

No. 3 - 2017

RSNN
Regulatory Science Netwerk Nederland

Dear Reader,

This is the third Regulatory Science Network Netherlands (RSNN) Newsletter. The RSNN, a network for experts from academia, government, the pharmaceutical industry, patient organisations and others involved in regulatory activities related to drug development, aims to facilitate activities in the field of Regulatory Science in the Netherlands by stimulating dialogue and collaboration, and sharing information and methods. The RSNN is aligned with other European platforms active in the field.

The RSNN Newsletter informs participants and stakeholders of activities and developments in the discipline. In this edition you will find a first impression of the RSNN Workshop 'Beyond the current clinical endpoints' held on July 6, 2017, and announcements of upcoming meetings. We also present the standing executive - and steering committee of the RSNN.

WORKSHOP 'BEYOND THE CURRENT CLINICAL ENDPOINTS'

How can we improve the selection and use of challenging endpoints such as the 'established' 6-minute walk test (6MWT) or the less well-known ones such as the Goal Attainment Scaling (GAS)?

This was the key question of the workshop held on July 6 2017 and a continuation of the theme of the most recent RSNN meeting at the 2016 FIGON Dutch Medicines Days. More than 60 participants came to the 'Muntgebouw' in Utrecht and had a very inspiring meeting. Besides the keynote lectures there was ample opportunity for both formal and informal networking during the workshop, drinks, and an animated dinner.

OPENING AND KEYNOTE LECTURES

Prof. Dr. Bert Leufkens, Chairman of RSNN, opened the workshop. In his introduction, he stressed the importance in clinical research of using endpoints that have clinical relevance, since only this will lead to outcomes that are relevant for patients. To achieve this, we need to look "beyond the current endpoints" (as the title of the workshop said), show courage (to leave the beaten track), and listen to all stakeholders.

And this was exactly the aim of the workshop! Experts from patient communities, academia, industry, health technology authorities and regulatory authorities gathered to discuss how we can improve the selection and use of challenging endpoints.

To support these discussions, the workshop started with four lectures that addressed the topic from different perspectives: the investigator, the regulator, the industry, and the reimbursement sector.

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FIGON

SAVE THE DATE:
2 October, 2017

RSNN SESSIONS AT THE 2017 FIGON DUTCH MEDICINES DAY

Congres centrum De ReeHorst
Bennekomseweg 24
EDE, The Netherlands

www.figondmd.nl

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12 October, 2017

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CALL FOR AGENDA TOPICS: YOUR INPUT IS NEEDED!

[more on page 8]

JOIN THE RSNN – The RSNN is an open network

You can join by contacting:
Daphne Houtkamp
email: d.houtkamp@cbg-meb.nl

We also like to invite you to our LinkedIn group at:
https://www.linkedin.com/groups/8559430

RSNN SESSIONS AT THE 2017 FIGON DUTCH MEDICINES DAY

Regulatory learning from disease interception

As diagnosis, treatment options, and indications start to become increasingly advanced (and complex), opportunities are created to intervene in disease states at earlier time points. At the same time, this creates a need for prognostic biomarkers and companion diagnostics.

Early intervention in disease could allow for novel drug-therapies to be initiated, for example statins or PCSK-9 inhibitors in cardiovascular disease. Alternatively, early diagnosis could lead to novel treatment regimens, for example in oncology turning it from terminal diseases to a slowly progressing or even maintenance disease.

Emerging technologies, such as macrobiotic transplants, blur the line between drug and surgical intervention.

But what are the challenges for regulation? How do we determine benefit risk for these new indications where disease is not well established and/or refractory? How do we stratify the patient groups for a clinical trial? What endpoints do we use?

These are the questions that will be addressed by various speakers at the next Regulatory Science Sessions that will be held at the FIGON Dutch Medicines Days on Monday October 2, 2017.

THE PROGRAMME OF THE DAY IS:

MORNING SESSION:

09.00 – 09.10	Setting the Scene - Dr. Christine Gispen-de Wied, MEB/vice-chair RSNN
09.10 – 09.35	Gut and Microbes - Prof. dr. Ed Kuijper, LUMC
09.35 – 10.00	Brain and Amyloid - Prof. dr. Philip Scheltens, VUmc
10.00 – 10.25	Metabolic Syndrome - Prof. dr. Frank Visseren, UMCU
10.25 – 11.00	Plenary discussion

AFTERNOON SESSION:

14.30 – 14.55	Industry perspective - Paul McCleverty, EMEA head of Oncology, global regulatory affairs, Johnson & Johnson
14.55 – 15.20	Regulatory considerations - Prof. dr. Bert Leufkens, UU/chair RSNN
15.20 – 15.50	Plenary discussion/wrap up

Date: 2 October, 2017
Venue: Congres centrum De ReeHorst
Bennekomseweg 24, Ede
The Netherlands

For more information visit: **www.figondmd.nl**

The first speaker was **Prof. Dr. Kit Roes** (Julius Center/ UMCU/MEB). Kit, as a statistician, not only used this opportunity to share his views on the future of clinical endpoints, but also to shed some light on how the designs of clinical trials, their methodology, and statistical principles might look in the years to come. Kit kicked off with some examples of clinical endpoints, like single endpoints and (true) surrogate endpoints, which can predict clinical outcome. He used these examples as a background to his plea for the need of new concepts in clinical trials; for instance, the need to use multiple variables and sets of relevant endpoints. To make this change, we first must have a better understanding of the biology of a disease. In mitochondrial disease, a condition with a variety of different symptoms, this typically could lead to the use of different sets of endpoints. Secondly, we must also address what is important to patients! For example in Duchenne Disease, it is more important for some patients to be able to work on a computer than to be able to walk, something that can be measured for each patient by using the Goal Attainment Scale (1).

The next speaker was **Dr. Violeta Stoyanova** (COMP-EMA/MEB). Using two examples, she illustrated how complicated the task of the assessors can be, since the value of an endpoint differs with the stage of the disease and the type of treatment. Also, in the process of assessing a new therapy or compound, we like to compare it with the actual standard and therefore we also tend to stick to the standard endpoint, which hinders the use of new endpoints. This is perfectly illustrated by the expanding use of the 6MWT (Box 1); having been developed as an endpoint for pulmonary hypertension trials, it is now used in numerous trials in other diseases, despite the fact that it is not the most optimal endpoint for all patients nor in all stages of a disease. Properly considering feedback from patients will allow us to move in the right direction when trying to improve the usage of existing endpoints and increase the relevance for patients at the same time.

Struggles with the use of endpoints are also not unfamiliar to the pharmaceutical industry, although according to the next speaker, **Henk Kamsteeg** (Janssen Biologics), the perspective is a different one. Of course, pharma wants to develop treatments that will help patients, but at the time, the main aim is to get a product registered and to get it to the patient.

[BOX 1] SIX MINUTE WALK TEST (6MWT)

During the workshop, the Six Minute Walk Test (6MWT) was used as the example of an endpoint that over the years has stirred up a lot of discussion. The 6MWT is widely used to estimate the effectiveness of interventions in numerous diseases such as osteoarthritis, pulmonary fibrosis, heart failure, COPD, Duchenne Muscular Dystrophy, and Fabry's Disease. The reasons for its use vary across diseases: as surrogate for the clinical outcome, as accepted standard or as "the best we have". The 6MWT has been a good measure of physical performance and has successfully been used in patients with pulmonary arterial hypertension. Contrary to this, its use in neurodegenerative diseases has sparked much discussion since it is questionable whether distance can readily be translated to the most relevant complex functional outcomes. For instance, in Duchenne Muscular Dystrophy, the 6MWT is often used to evaluate potential new treatments, but this outcome is irrelevant for patients who are already in a wheelchair.

In reality, this sometimes means that the results of clinical trials, in terms of their clinical endpoints, do not match the relevant outcomes for the patient. However, such a focus on the use of endpoints that are only relevant from the perspective of one stakeholder can be detrimental to the development of new treatments. This was illustrated by an example taken from Henk's own experience: the development of a new drug for multiple sclerosis which sadly came to an end because of the chosen clinical endpoint: '10 years more delay to wheelchair'. This endpoint, in the opinion of an insurance company, was of no relevance to them and therefore, before the drug was even registered, they stated that they would never reimburse for the treatment.

The last speaker was **Dr. Jacoline Bouvy** (NICE), who shared her thoughts from an Health Technology Assessment (HTA) perspective, in particular on how NICE develops its advice for reimbursement and coverage of (new) treatments. Central to this process are cost-effectiveness, the impact on quality of life (QoL) and life expectancy, and the reduction of decision (on reimbursement) uncertainty. This is clearly different from the regulatory process and is one of the main reasons why a HTA tends to look at different endpoints from those already considered by the regulators. A complicating factor is the country-specific HTA approach in the EU because of the different Health Care Systems. Jacoline concluded that from her perspective the issue is not the endpoint: product, price, cost-effectiveness, and data on QoL or life expectancy are far more important

WHITE PAPER

Based on the outcome of the workshop, the pros and cons of current, additional, and novel endpoints will be mapped. This stakeholder and criteria map will be used to identify both opportunities and gaps in using novel endpoint concepts, and to provide input to key criteria for endpoint definition and selection. The latter could facilitate discussions on accepting new endpoints and could potentially contribute to the development of clinical trial guidelines. It may also form the basis for systematically including the different stakeholder's perspectives in the early stages of trial design. It is the intention of the RSNN to share the stakeholder and criteria map within the field, preferably with a white paper and a subsequent peer reviewed publication.

WORKSHOP AND PLENARY DISCUSSION

After the four lectures, it became clear to those in the room that all stakeholders are needed at the table in order to overcome the hurdles that will be encountered on the way to better endpoints. It was therefore not a surprise that all participants eagerly joined one of the four breakout panels. Each of these four panels had a different focus (regulatory, HTA, statistics and methodology, and the industry perspective) and was led by one of the speakers, who were given a specific set of questions based on a given perspective. The participants were asked to provide their thoughts relative to this perspective and give suggestions on how to improve the clinical relevance/ applicability of given endpoints like the 6MWT, the Goal Attainment Scale or biomarkers.

The feedback from the breakout session was extensive and was summarised by the session leads and Peter van Meer. In general it was recognised again that there is a need for more alignment of expectations between the different stakeholders. It was proposed that more attention should be given to a more holistic view of endpoints instead of focussing on one single endpoint, and to use more generic endpoints in addressing certain disease areas or clusters of diseases. Importantly, when thinking of choosing an endpoint we should try to formulate a comprehensive, consistent hypothesis on how the treatment works and how this

REFERENCES

1. Gaasterland CMW, Jansen-van der Weide MC, Weinreich SS, van der Lee JH. A systematic review to investigate the measurement properties of goal attainment scaling, towards use in drug trials. BMC Med Res Methodol 2016; 16: 99.

will affect multiple endpoints. A plea for learning by all the stakeholders was made as well: we should do more with the lessons learnt from tackling each successive hurdle in the process from registration to reimbursement decisions. One of these lessons, for example, is that patients should be involved at an earlier stage of the process of developing guidelines. One should also keep in mind that a single significant endpoint is not the basis for registration. The overall profile of a product plays a more important role. Endpoints though are critical, in particular when the volume of data is limited. Finally, it was proposed to integrate the registration and reimbursement processes; in other words to use a core set of criteria and agree on them before you start your development programme or individual trials. At this stage even insurance companies could be involved and asked for their commitment to reimburse based on the agreed endpoints of trials.

During the very lively plenary discussion that followed, points of view were sharpened. Henk Kamsteeg noted that we are moving to more personalised medicines and therefore we should also move to a more personalised approach when defining endpoints as well. Violeta Stoyanova stated that in the process of identifying and agreeing clinically relevant endpoints, we also should think about how to implement these in a clinical study in terms of time and numbers of patients needed.

Defining better endpoints means also that one should be able to provide certain treatments earlier to patients and in that context the concept of adaptive pathways was brought up by one of the attendees: is it an option to think of the 'gradual introduction' of a new drug to the market? A central question with such a scenario is how one can guarantee the necessary level of clinical evidence on safety and efficacy.

According to Christine Gispen-de Wied, who moderated the discussion, things are not black or white; while developing and implementing the concept of adaptive pathways, we are not lowering the standards in licensing. This is also true of our search for and use of more and multiple endpoints that are of clinical relevance and of benefit to the patient. Or in the words of Pauline Evers (Stichting Leven Met Kanker): we need statistical evidence as a basis, but we are adding to that the idea of clinical relevance; we should combine both and look at the whole picture.

Coming to the 'end(point)' of the discussion, Bert Leufkens asked the panel for their advice on what we could learn from a regulatory point of view and what would be the next step. Violeta suggested that we should make more use of the knowledge on biomarkers in search of subsets of populations that will or will not respond to a certain treatment. Kit advised starting with what we can change within the current system instead of trying to change the whole system and Henk repeated the need to focus on endpoints that are relevant for the patient. Christine concluded that Bert, as the chairman of RSNN, quite rightly addressed the regulatory learning aspect because the RSNN network provides the platform to do so with the aim of improving the regulatory process and thereby improving the benefit of treatments for patients at the earliest stage possible.

DINNER SPEECH

In the tradition of the RSNN workshops, discussion continued during dinner, interrupted only by a dinner speech. This time Marc Kaptein, medical director at Pfizer and Yvonne Schuler, researcher at AMC/UvA, accepted the invitation to take the stage. Marc compared the 'pharmaceutical ecosystem' with a rainforest: both are very complex ecosystems in which any change made by an individual will affect all others; translated to the topic of the day: when decisions are made about the need for clinical endpoints, we need to reflect on the effect on the entire ecosystem. Basic safety and efficacy of new drugs needs to be studied, however, decreasing risk and increasing knowledge about new drugs come with (high) costs. Yvonne made a plea for the involvement of patients in the search for the right endpoint(s). She illustrated her appeal with the example of a case in which a new drug for an orphan disease was not reimbursed because the endpoint wasn't relevant for the disease. She expressed her hope that in the future, we can bridge the gaps together.

In the words of Christine this was the right moment to thank all contributors and attendants for a very inspiring day. There is still a lot of work to do, and by working cooperatively we will achieve the results we want.

PRESENTATION RSNN POLICY PLAN AT THE 2017 FIGON DUTCH MEDICINES DAY

In the last two and a half years, the RSNN activities were supported by several stakeholders, in particular the Dutch Medicines Evaluation Board. In this period, several scientific meetings were organised, brainstorm sessions were held aimed at setting up - and further developing the network, and a first policy plan was developed (a summary is available at http://figon.nl/nl/Rsnn).

It is the wish of the executive board of the RSNN to initiate the next steps and extend its collaborations with partners (academia, the government, pharmaceutical industry, patient organisations, and other disciplines) who are involved in regulatory activities related to drug development; make these relationships sustainable; and together with these partners share the responsibility for the further (financial) support of the RSNN.

In February 2017, Lygature was asked to support these next steps by adapting and extending the RSNN policy plan and by approaching potential partners.

The outcome of this work will be presented at the FIGON Dutch Medicines Days, 2-3 October 2017, and at a Lygature 'Partnerships MeetUp', on 12 October 2017. More information on this last meeting can be found at http://events.lygature.org.

MEET THE STANDING RSNN EXECUTIVE - AND STEERING COMMITTEE

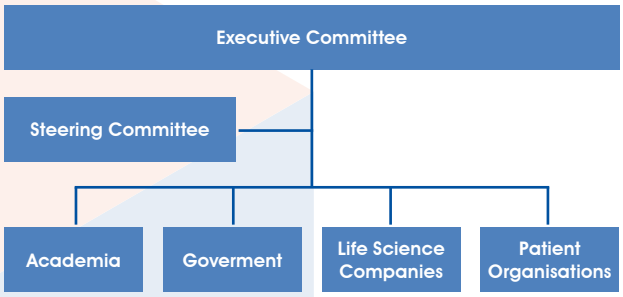
At the RSNN inaugural meeting on October 5 2015, the organisational structure of the RSNN was established and since that time several people have taken up the responsibilities of the executive and steering committee.

For the 7 members of the executive committee these responsibilities are related to the main day-to-day activities, the organisation of events, external communications e.g., this newsletter), and the further development of the network. This committee meets several times a year and is chaired by a member the Medicines Evaluation Board.

Current members are:
- Dr. Sjaak Bot (Johnson & Johnson)
- Dr. Christine Gispen-de Wied (UMCU, Medicines Evaluation Board [MEB])
- Prof. Dr. Bert Leufkens (Chairman, University of Utrecht [UU])
- Dr. Peter van Meer (MEB)
- Prof. Dr. Kit Roes (Julius Center University Medical Centre Utrecht [UMCU], MEB)
- Just Weemers (Pfizer Nederland)
- Prof. Dr. Dick de Zeeuw (University Medical Center Groningen)

The 9 members the RSNN steering committee support the RSNN executive committee. For example, the members provided input to the policy plans, and when asked advise on topics (scientific, regulatory, societal) that are of importance to the RSNN.

The members are:
- Dr. Agnes Kant, Lareb
- Prof. Dr. Aletta Kraneveld, UU
- Andre Broekmans, Lygature
- Ienke Brombacher, Xendo
- Dr. Marc Koopmanschap, Erasmus University Medical Center
- Dr. Peter Mol, MEB, University Medical Center Groningen
- Pieter Stolk, UU
- Dr. Remco de Vrueh, Lygature
- Dr. Wouter Boon, UU

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CALL FOR AGENDA TOPICS: YOUR INPUT IS NEEDED!

One of the goals of the RSNN is to bring all stakeholders to the table, to stimulate open conversations, and support steps towards the changes needed in the regulatory process.

RSNN's agenda is driven by developments in the life science area and needs your input. We therefore call for agenda items that you feel should be shared and discussed with colleagues in the field of regulatory science. Currently, biomarkers, precision medicine, and endpoints are topics we focus on, but we are sure that there are more.

Please share your ideas and suggestions using the contact details at the end of this newsletter.

The development of the newsletter was supported by Terminal 4 Communications (www.t4comms.com)

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