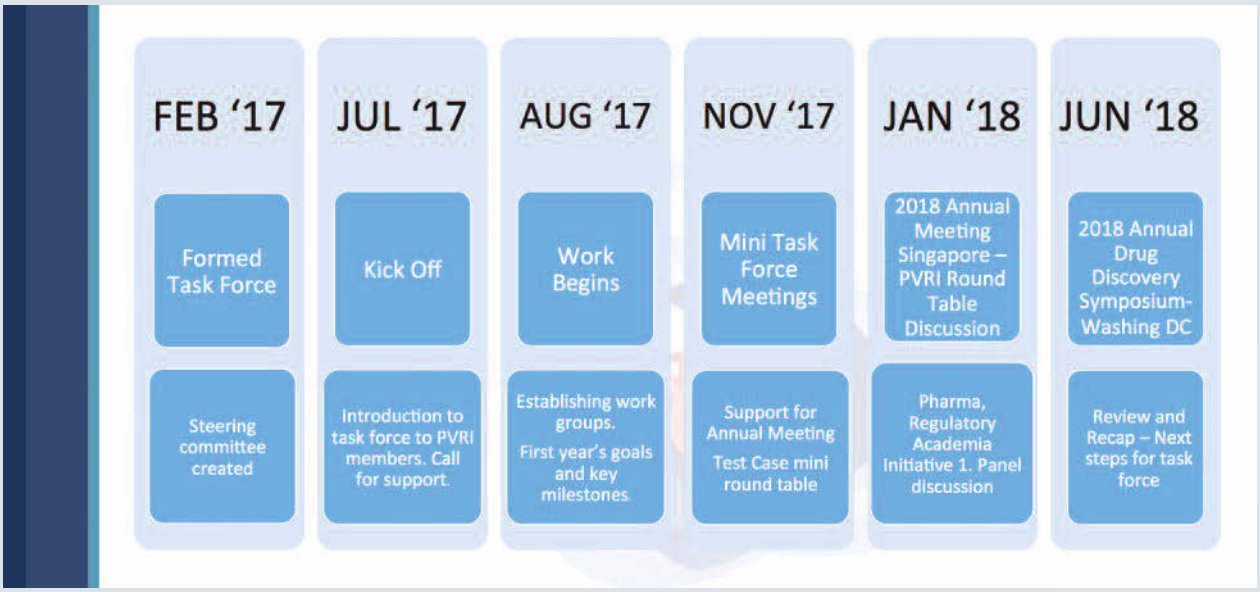
PVRI **Pharma Report 2017**

Peter Fernandes, Sylvia Nikkho & Lawrence Zisman

The aim of PVRI Pharma Task Force is to investigate possible options and solutions to ensure the approaches used for small population clinical trials for developing orphan drugs in the field of rare diseases are effectively directed towards ultimately making safe and effective therapies available to these critically ill patients in a timely manner.

Key Milestones Chart 2017 - 2018 Road Map



A special focus of the PVRI Pharma Task Force is to apply these learnings first towards pulmonary arterial hypertension (PAH), a rare disease with a still significant unmet need.

In order to maximise the scarce resources available for recruiting subjects for clinical trials in this rare disease, there is a critical need to coordinate and harmonise innovative approaches through; clinical trial designs, endpoints, biomarkers, translational research, and enrichment strategies.

The PVRI Pharma Task Force's mission is to create and to provide platforms for early and continuous dialogue on innovative clinical and regulatory development strategies, where there is free and open discussion and sharing of creative ideas between pharma, academics and regulators worldwide.

In order to further encourage and support this mission, a PVRI Pharma Steering Committee (SC) was formed in February 2017. Members of this SC include Peter Fernandes (Bellerophon as Lead), Sylvia Nikkho (Bayer as Co-Lead), Lawrence Zisman (Pulmokine), Andrew Nelsen (United Therapeutics) and Jonathan Langley (GSK). This SC will foster and facilitate the creation of platforms to gather the relevant information and organise workshops with pharma, academia and regulators to discuss and harmonise possible options and solutions in a non-competitive manner.

At the PVRI meeting in Berlin in July 2017, there were two Initiatives rolled out to the broader PVRI attendees, these included:

INITIATIVE 1

Harmonise innovative approaches through clinical trial designs, endpoints, biomarkers

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Endpoint Think Tank

The kick-off meeting of the PVRI Pharma Task Force Meeting on clinical endpoints, organised and facilitated by Sylvia Nikkho, took place on 11 September 2017 on the margin of the ERS conference in Milan. The meeting was well attended with 16 international participants of patient organisations, academia and pharma industry. The group has monthly telephone conferences to discuss the way forward until the PVRI Annual World Congress, which will take place in Singapore in January 2018, and to define the steps beyond.

Objectives agreed upon

The work stream is a **Think Tank** on **Endpoints** where there is free and open discussion between representatives of patient organisations, academia, regulatory agencies and pharma worldwide.

Patient focused areas identified

- Established endpoints: Weigh limitations versus advantages
- Composite endpoints: Look at improvement rather than on deterioration. Here the focus is on what is of interest to the patients, and which endpoints can shorten development timelines to bring novel treatments sooner to the patients.
- Patient reported outcome: Suitability as secondary and potentially primary endpoints
- Reimbursement: Take into consideration the view of agencies assessing the benefit to the patient

Biomarkers

Overview: There is substantial effort being undertaken by collaborating PAH centres in the US, UK, and Europe to generate high throughput genomic, proteomic, and metabolomic data sets from the PAH population. Sample collections for high throughput screening to identify biomarkers could be integrated with any new phase 2 trial in PAH. Other biomarkers based on PAH pathophysiology have been reviewed.

Key questions include

A **Circulating Biomarkers:** What are the acceptable criteria for a circulating PAH biomarker? What clinical endpoints should be used to determine if a biomarker is applicable? What incremental value is needed in addition to current biomarkers (incremental value over and above NT-pro-BNP for example)? How will high throughput analyses be incorporated in phase 2 and 3 clinical trials? What are the regulatory, logistic, and management issues? A goal of this initiative is to provide a summary of current on-going PAH networks, and contact information .

B **Imaging:** Lung biopsy in the setting of pulmonary hypertension is contra-indicated. New approaches to tracking response to novel therapies in PAH are needed. Potential novel imaging modalities that could be included in phase 2 trials are high resolution CT vascular imaging and PET scanning.

C **Cardiopulmonary haemodynamics:** Should studies of PAH continue to include assessment of cardiopulmonary haemodynamics, including measurement of pulmonary artery pressure? Is there a role for continuous monitoring of PA pressure (i.e., CardioMEMS™ device) in future PAH trials? What are the technical, regulatory, safety and cost issues? Should pulmonary vascular resistance be considered a "biomarker" or an "endpoint"?

It is known that RV function has prognostic implications; should additional measures of RV function be included in phase 2 trials of new treatments for PAH, such as measurement of RV strain? The six-minute walk distance has been a mainstay of clinical trial performance in PAH. Should additional measures of cardiopulmonary exercise capacity be included in future phase 2 and 3 trials, such as measurement of VO2max?

Clinical Trial Designs

Background: Traditional drug development with large sample sizes clinical studies with clinical outcome driven endpoints (ie M&M or TTCW or 6MWD) are no longer practical for rare diseases like PAH in adult and paediatric populations. Despite the availability of over 14 PAH treatment options available today, the characteristics of the disease and the key factors that manage or predict disease progression and survival is unclear. Clinical trial designs and endpoints are still not optimised and so provide very limited useful information. This translates into clinicians being left to make difficult treatment choices that are often unguided or based on clinical experience and / or relying on the limited clinical trial outcomes alone. The common goal as an outcome from the Think Tank for Endpoints and Biomarkers initiative that will feed into the Clinical Trial Designs initiative will be to:

- Learn from the experience and data generated from the 14 PAH treatment options.
- Identify a reliable and practical biomarker to discern efficacy in both adult and paediatric populations for PAH.
- Design suitable clinical trials for establishing efficacy in both adult and paediatric populations for PAH.

Based on initial interests and support from academics, pharma and regulators, the following sub-topics will be explored further as a lead up to the Annual Congress in Singapore:

- Phase II Design/Early Proof of Concept - focus on "Pharmacometrics (or Biosimulation for EU) Studies" and "Functional Respiratory Imaging (FRI) Studies"
- Innovative Phase 3 studies designs - focus on "Randomised Withdrawal and Early Escape Studies"

INITIATIVE 2

Matching industry projects/interests with individual investigator interests and core strengths

Andrew Nelsen & Jonathan Langley

The goal of this initiative is to initially provide a searchable database to match the research interests of both academia and industry.

At the Berlin meeting in July 2017, an overview and summary document articulating research interests amongst industry partners and academic members was presented. This document included top line areas of interest as well as contact information on sample cases. These cases present the concepts of this research interest document for feedback and discussion, with the objective of dissemination to the broader PVRI Industry-Academia.

Following the feedback, the current goal is to update the members section of the PVRI website to enable the profile pages to be updated with a searchable selection of areas of interest, as well as a freetext to add areas not covered. Individual and industry members will be able to update their profile page and use a search function to find those specific in areas. To enable this, the website will need to be developed. The PVRI team is assessing the requirements and timelines and these will be communicated in the future.

We can get more sophisticated as we develop this tool over time, potentially developing it to assist in the planning for clinical research in PVD. We look for your participation in the population of the member profiles moving forward and to take this to the next level.