PVRI **Innovative Drug Development Initiative (IDDI) Report 2019**

Peter Fernandes, Sylvia Nikkho & Paul Corris



The Innovative Drug Development Initiative, formerly known as the PVRI Pharma Task Force, was established in January 2017 under the leadership of Paul Corris (PVRI), Sylvia Nikkho (Bayer) and Peter Fernandes (Bellerophon).

Its mission is to provide a platform for academia, the pharmaceutical industry and drug regulators to openly discuss questions surrounding the future of trials comprising novel drugs. It encourages early and continuous dialogue with all stakeholders, including the patient's perspective, on innovative clinical and regulatory development strategies, with the ultimate aim of finding new ways to fight and treat pulmonary vascular disease and pulmonary hypertension. The IDDI is an integral part of the PVRI's strategic mission and four backbone initiatives.

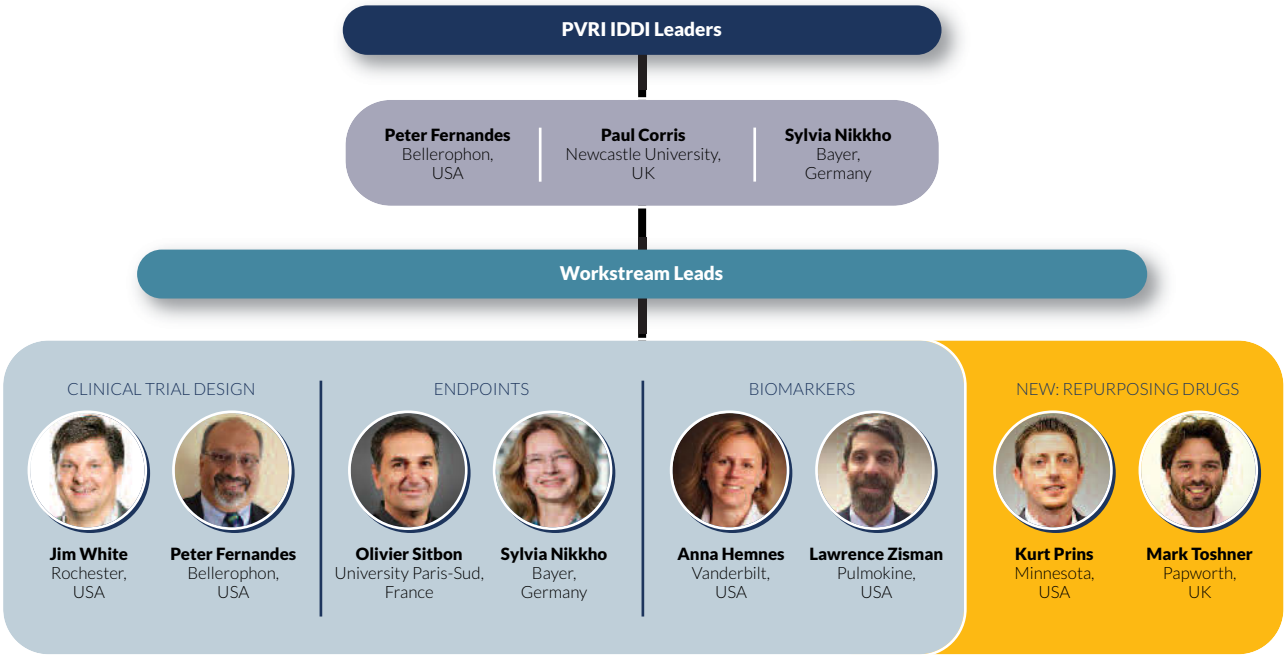
The current aim of the IDDI is to establish a series of position papers, developed by each IDDI workstream. These will be released as abstracts, posters, oral presentations and peer-reviewed articles, which will be published in the PVRI's journal Pulmonary Circulation. The purpose of these statements is to enhance global understanding of the disease and provide a valuable insight into the complexities surrounding new drug discovery in this disease field.

IDDI Workstreams

During 2019, an additional workstream on Repurposing Drugs was formed, in addition to the already established three workstreams of Endpoints, Clinical Trial Design and Biomarkers. All four workstreams are interlinked and mutually supportive, and are led by an academic and a pharma representative:

- **Clinical Trial Endpoints** led by // Olivier Sitbon UNIVERSITY PARIS-SUD, FRANCE & // Sylvia Nikkho BAYER, GERMANY
- **Clinical Trial Design** led by // Jim White UNIVERSITY OF ROCHESTER, USA & // Peter Fernandes BELLEROPHON, USA
- **Biomarkers** led by // Anna Hemnes VANDERBILT UNIVERSITY, USA & // Lawrence Zisman GOSSAMER BIO, USA
- **Repurposing Drugs** led by // Mark Toshner UNIVERSITY OF CAMBRIDGE, UK & // Kurt Prins UNIVERSITY OF MINNESOTA, USA

PVRI IDDI Structure



Highlights during 2019

During the Gala Dinner of the PVRI 13th PVRI Annual World Congress on PVD, which was held in Barcelona, Sylvia Nikkho and Peter Fernandes were presented with the PVRI Certificate of Excellence 2018 Award for their dedicated and visionary leadership of the IDDI. This prestigious award, which celebrates the most active leaders of a PVRI Task Force, was presented by the PVRI Chief Scientific Medical Officer, Paul Corris, who received the 2018 PVRI Lifetime Achievement Award.

Activities during 2019

Two 'IDDI Open Forum' meetings were held during the year, attracting audiences of over 100 participants including representatives from academia, patient organisations, regulatory agencies and the pharmaceutical industry. Stimulating presentations and interactive discussions were held at the:

- PVRI Annual World Congress, Barcelona, Spain, January 2019
- PVRI Drug Discovery & Development Symposium, Paris, France, July 2019

In addition, regular telephone conference calls were held throughout the year by each of the respective workstreams and a meeting of the IDDI workstream leaders was held during the ERS Conference in Madrid in September 2019 to monitor progress on the publication of position statements.

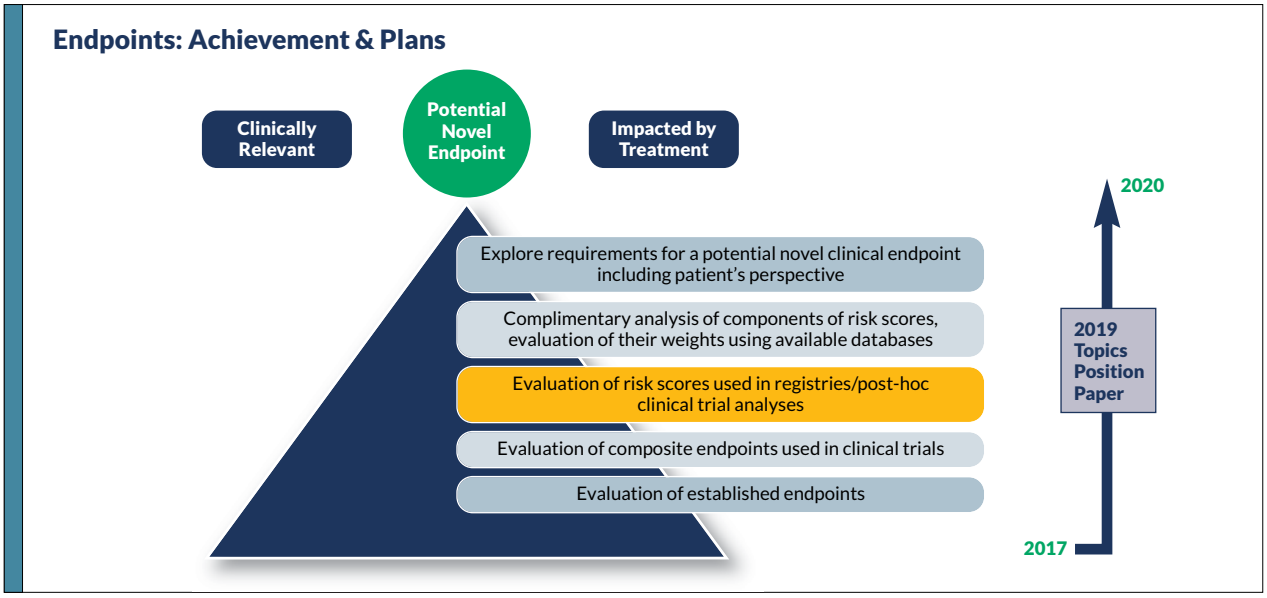
Clinical Trial Endpoints Workstream

The workstream on novel endpoints, chaired by Olivier Sitbon and Sylvia Nikkho, includes 27 members and investigates the potential role of utilising composite improvement endpoints, as well as risk scores, as novel clinical endpoints in PAH clinical trials.

In Barcelona, the endpoint break-out session was led by Sylvia Nikkho and Olivier Sitbon. The work was supported by Paul Corris, Christian Meier and Werner Seeger. It focused on composite improvement endpoints, which were already used in clinical trials and allowed individual responders to be identified in a much shorter period of time in comparison to time to clinical worsening endpoints, decreased the placebo response and thereby required a smaller number of patients. However, it was discussed with the participants that current dual or triple background therapy should be considered which may diminish the effects of the treatment, and subsequently may require enrichment strategies for future trials.

Vibrant discussions arose relating to the choice of certain risk scores in endpoints for both Phase 2 and 3 trials, during the IDDI meeting in Paris in July 2019. Pro and con discussions of risk scores as potential clinical endpoints and statistical aspects of incorporating risk scores into clinical trials were presented by Olivier Sitbon, Chunqin (CQ) Deng and Mardi Gomberg-Maitland supported by Raymond Benza and Harrison Farber. While risk scores were proven to be good prognostic tools, as well as predictors of outcome and survival in registries, the discussion of the participants focused on whether and how best these could be clinically meaningful and discriminative of treatment effects based on available post-hoc clinical trial analyses. As for composite improvement endpoints, it was agreed that in future PAH trials treatment effects needed to be compared in addition to dual or even triple therapy.

The aim of the planned publication is to discuss the potential of composite improvement endpoints, as well as risk scores, as novel clinical endpoint in trials, while considering established clinical endpoints as taken care of by Marion Delcroix, Joanna Pepke-Zaba and Gérald Simonneau in the important context of the regulatory and patient's perspective, and close interaction with the members of the other workstreams.



Clinical Trial Design Workstream

The workstream on Novel Clinical Trials, chaired by Peter Fernandes and Jim White, discussed the following topics during 2019 with focus on the use of actigraphy to monitor changes in physical activity (PA) and its evolving role in pulmonary hypertension clinical drug development as a primary regulatory endpoint gaining acceptance by regulators for Phase 3 clinical studies.

Patient focused drug development incorporates the VOICE OF THE PATIENT (VOP) and ultimately places the patients first when considering the risk and benefit of treatment. Discussions with patient focus groups have reported that daily physical activity is most meaningful to those living with this disease (FDA PFDD Meeting 26 September 2014) and aligns with to every-day management of their illness.
The objective measurement of PA monitoring devices offers a reliable measure of a patient's daily activity that can be utilised to measure this clinically meaningful outcome. The Food & Drug Administration (FDA) in the USA has recently accepted physical activity as measured by actigraphy as an acceptable regulatory endpoint for a Phase 3 study in IPF. In order to apply this endpoint to other cardiopulmonary disease clinical study designs, the development team will need to deliberate on key questions outlined below:

- **What physical activity are we assessing in the targeted patient population?**
- **What are the time points or study visits that these will be assessed?**
- **What is the minimal wear time required?**
- **How will patients be instructed - training?**
- **What is the evaluable wear time to be assessed - account for missing/evaluable data?**
- **What is the minimal % change in PA that is considered meaningful MCID?**
- **How will MCID be pre-determined/pre-specified?**
- **What other qualitative data is needed to support this MCID - i.e. PROs?**

Further working group discussions are planned to outline and deliberate on the role of innovative trial design, including the use of better stratification of patients at trial enrolment, enrichment strategies, adaptive approaches to trial design and withdrawal studies. The IDDI workstreams will collaborate on harmonising their approach towards developing a Master Protocol with actigraphy as a primary endpoint to facilitate its implementation into future cardiopulmonary drug development programmes.

Biomarkers Workstream

The working group on Novel Biomarkers, chaired by Lawrence Zisman and Anna Hemnes, explores this rapidly developing scientific area. The challenges of both clinical trial design and novel surrogate endpoints in Phase 2 studies of anti-proliferative approaches are being considered.

In Paris, the Biomarker subteam provided an overview of biomarkers for PAH. An emphasis was placed on the potential use of biomarkers to predict response to a therapeutic intervention. New approaches to circulating biomarkers were discussed, as well as imaging of the right ventricle and pulmonary vasculature. The European Medicines Agency's (EMA) view of surrogate endpoints was reviewed and it was recognised that there are currently no validated biomarker surrogate endpoints that meet regulatory criteria for use as approvable endpoints in PAH. Indeed, even NTproBNP does not meet the criteria for use as a surrogate endpoint based on EMA guidelines.

Nevertheless, NTproBNP, and potentially other biomarkers, have utility to examine the effects of therapy as well as use as prognostic indicators. For example, HDGF and GDH-15, in particular, are candidate biomarkers. Omic approaches to circulating biomarkers were reviewed, including genomics, transcriptomics, proteomics and metabolomics. An example from the field of proteomics was described wherein a panel of 9 proteins showed prognostic power independent of the REVEAL score. New approaches, such as the use of circulating exosomes, single-cell RNA sequencing, and cell free DNA were reviewed.

Imaging approaches to the right ventricle were discussed, including the use of RVEF from CMRI, and the use of RV strain from echocardiography. 3D reconstruction of the pulmonary vasculature from standard CT images has been reported. Use of 18FDG and 18FLT PET imaging have also recently been reported in PAH in relatively small studies. Hyperpolarised Xenon MRI of the lungs is a relatively new technique that allows examination of precapillary blood flow in a quantitative manner and may have utility in evaluating the effect of disease modifying agents in PAH.

Finally, the growing interest in the use of artificial intelligence and machine learning with potential applications to imaging and analyses of large omic databases were discussed.

Repurposing Drugs Workstream

Launched in February 2019, the workstream Repurposing Drug for PH is chaired by Mark Toshner and Kurt Prins and focuses on developing a roadmap for future drug repurposing, as outlined below.

Work stream members:

// Mark Toshner // Kurt Prins // Edda Spiekerkotter // Harm Bogaard

Introduction

- Introduction to the concept of drug repurposing.
- Place PAH/PH in the wider context of the drug repurposing landscape.
- Brief summary/history of repurposing in PAH.
- Outline of challenges - present and future.

Preclinical pipelines for drug repurposing

- Differing screen approaches.
- Success of screen vs targeted approaches.
- Challenges of animal and cell modelling.
- Use of genetic data.
- Mendelian randomisation.

Repurposing in the modern era

- Summary of clinicaltrials.gov data.
- Investigator-led studies are more likely to test novel therapeutic strategies, but these are single-centre and have difficulty recruiting and finishing.
- Industry-led studies are expensive, unlikely to test novel therapeutic strategies, but multi-centre and recruit and finish more often.

Challenges in repurposing and trial design

- Industry wide problems, not exclusive to rare diseases.
- The role of stratified vs non-stratified approaches.
- Evolving role of small biotech.

Objectives for 2020

The goal of the IDDI for the next year is to organise a meeting for all workstream leaders during the 14th PVRI Annual World Congress in Lima, Peru, on 31 January 2020, as well as an 'IDDI Open Meeting' immediately following the 7th PVRI Drug Discovery & Development Symposium, which will be held in Boston in June 2020. Emphasis during the year will be to finalise the individual position statements of each workstream ready for publication in Pulmonary Circulation. In addition, the IDDI should crystallise a unified vision for its future that will best serve all its members and diverse stakeholders in the long-term.

A note of thanks

We would like to express our sincere thanks to the dedicated leaders and members of all the four IDDI workstreams.

We greatly appreciate the support from all PVRI Roundtable members, who are part of the IDDI.