PVRI Pharma Task Force Meeting

Hyatt Regency -Bethesda, MD
July 9th, 2018

PVRI Pharma Task Force
UPDATE & INITIATIVES

Monday 9 July **18:30 - 21:00** Held in Conference Room

Welcome and Highlights: Paul Corris

Clinical Trial Designs

Moderator: Peter Fernandes

Topic: Innovative Clinical Study Designs for future studies for PH

1. Phase 2 a/b; FRI Imaging as a concept for "POC & Dose Ranging"
2. Phase 2b/3; Adaptive Study Designs, experiences, successes, failures to date with PH development studies and non-PH development studies.
3. Phase 3; Randomized Withdrawal Studies (RWS) for Phase 3 registration and Concept for Dose-Ranging-Adaptive-Withdrawal (DRAW) Studies.

Creating a database covering all 14 PAH approved therapies as a tool for testing the hypothesis for innovative endpoints. Can this be developed in collaboration with FDA, Academia and Pharma?

Endpoints

Moderator: Sylvia Nikkho

Topic: How best to develop future endpoints based on current experience

1. Summary of assessment of established and composite endpoints by the Endpoint Think Tank
2. Can risk scores be transitioned into future endpoints and what are the requirements?
3. Topics for a position paper and who volunteers

Wrap-up

Next steps and Q & A feedback from the audience.

Theme and Goal

- Theme of our Meeting.

  Academics, Patients, Pharma and Regulators Working Together to reach a Common Goal.

- The Common Goal.

  One of the goal of the PVRI Pharma Task Force is to investigate possible approaches for Small Population Clinical Trials for developing Orphan Drugs in the field of Pulmonary Hypertension → Pulmonary Vascular Diseases.

Mission Statement

Create and provide a platform for early and continuous dialogue on innovative clinical and regulatory development strategies, where there is free and open discussion between Academics, Patients, Pharma and Regulators worldwide.

Priorities for the next 3 to 5 years are to:

- **Create and facilitate a platform -- to allow discussion and harmonization of ideas between, Academia, Patients, Pharma and Regulators to build awareness on the disease and explore options to early diagnosis and treatment.**
- **Innovation -- Explore innovative and suitable clinical trial designs and endpoints for different forms of PH (first PAH and then PH-PF, PH-COPD....)**
- **Explore acceleration potential of clinical trials -- to bring novel Orphan Drugs as soon as possible to this critically ill group of Adult and Pediatric PH patient.**
- **Include the broad view -- of patients, caregivers and their advocacy groups**

PVRI Working Group

- **One of the goal of this working group is to investigate possible approaches for Small Population Clinical Trials for developing Orphan Drugs in the field of Pulmonary Hypertension.**

- **In order to maximize the scarce resources available for recruiting subjects for clinical trials in rare diseases, there is a critical need to coordinate and harmonize innovative approaches through:**

  - **Clinical Trial Designs (Moderator - Peter Fernandes)**
  - **Endpoints (Moderator - Sylvia Nikkho)**

Clinical Trial Designs (Moderator Peter) Status Update & Topics; Sub Team Members TBD

Innovative Clinical Study Designs for future PH studies (Overview on topics for discussion).

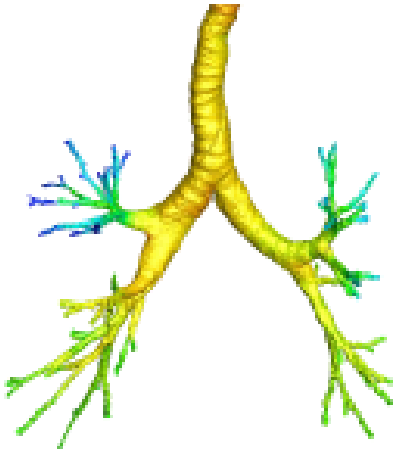
- Phase 2 a/b; FRI Imaging as a concept for “POC & Dose Ranging”
- Phase 2b/3; Adaptive Study Designs, experiences, successes, failures to date with PH development studies and non-PH development studies.
- Phase 3; Randomized Withdrawal Studies (RWS) for Phase 3 registration and Concept for Dose-Ranging-Adaptive-Withdrawal (DRAW) Studies.

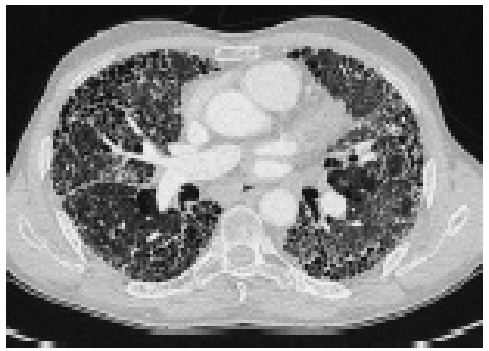
Concept for discussion: Creating a database covering all 14 PAH approved therapies as a tool for testing the hypothesis for innovative endpoints.

- Status of early developments and preliminary outcomes?
- Can this be developed further in collaboration with FDA, Academia and Pharma and Patient Advocacy Groups ?

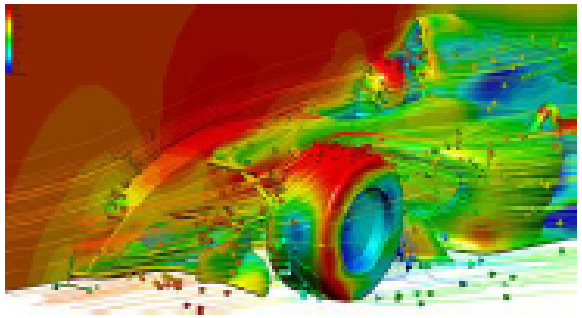
Concept for POC & Dose Range “Functional Respiratory Imaging (FRI)”

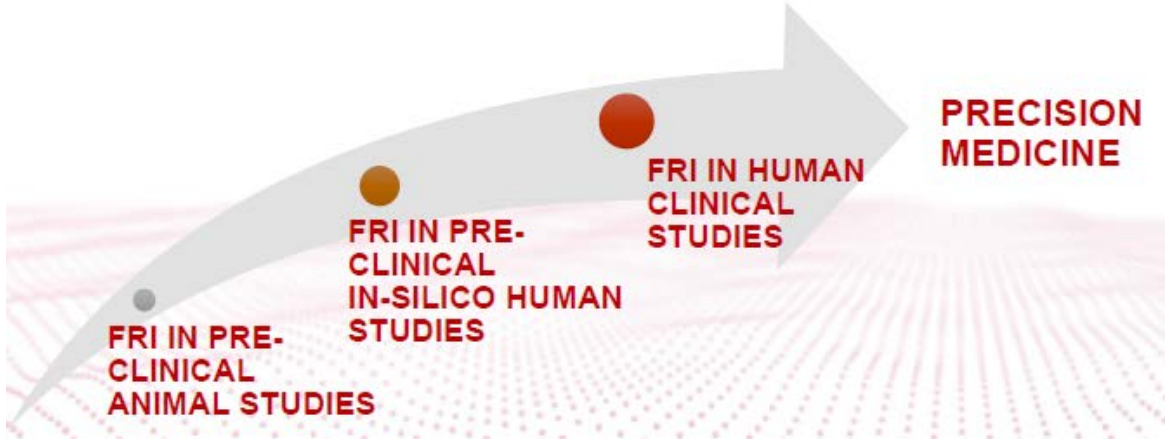
FUNCTIONAL RESPIRATORY IMAGING

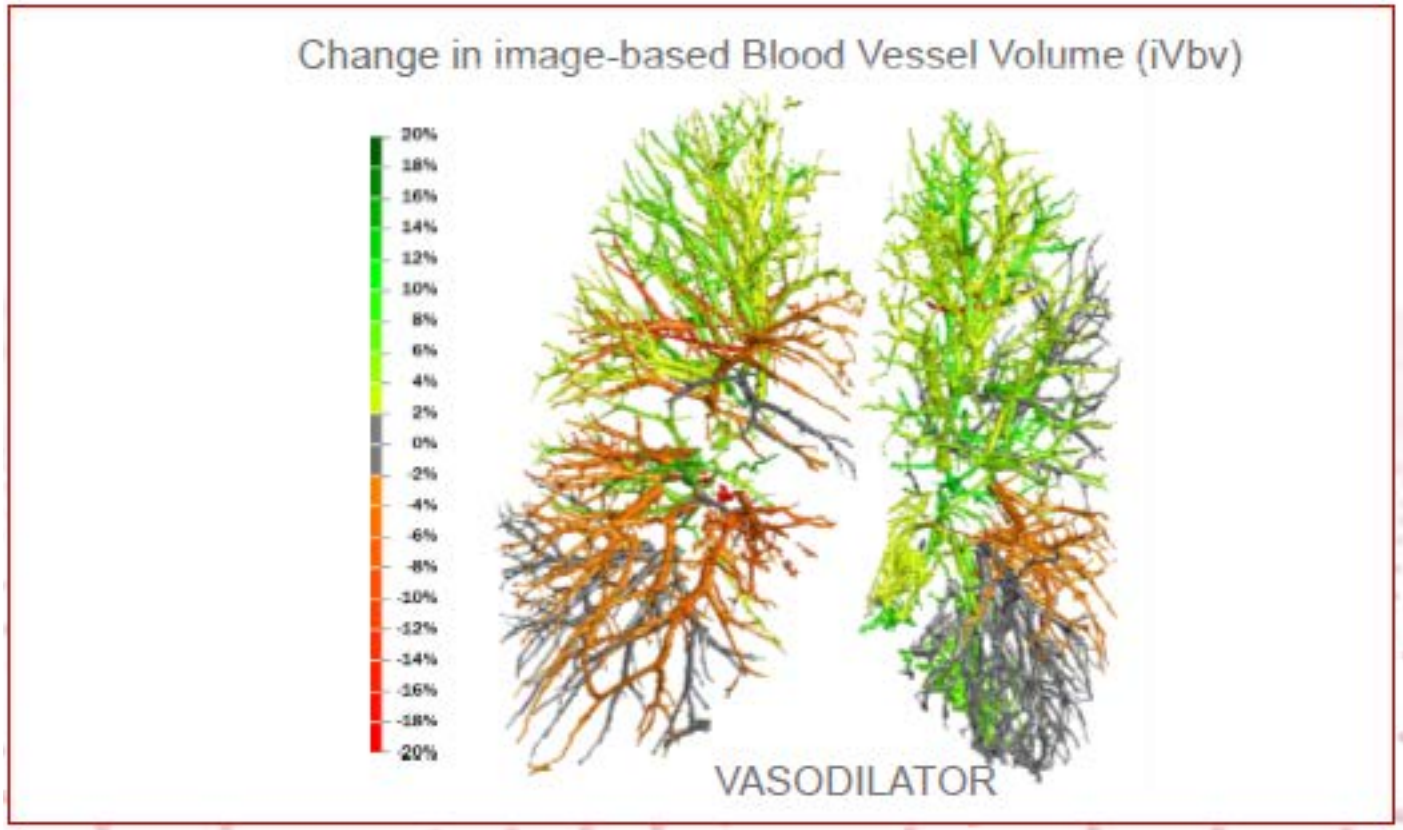




- Development of proprietary Functional Respiratory Imaging (FRI), a combination of
  - High Resolution CT Thorax (HRCT)
  - Flow simulations (Computational Fluid Dynamics, CFD)
- FRI provides regional information about
  - Lung structure (HRCT measurements)
  - Lung function (flow simulation)
- FRI is a sensitive biomarker that reduces
  - Study sample size
  - Study time
  - Overall Drug Development Cost
- FRI has the potential to seriously impact
  - Treatment accuracy and outcome
  - Overall Healthcare Cost

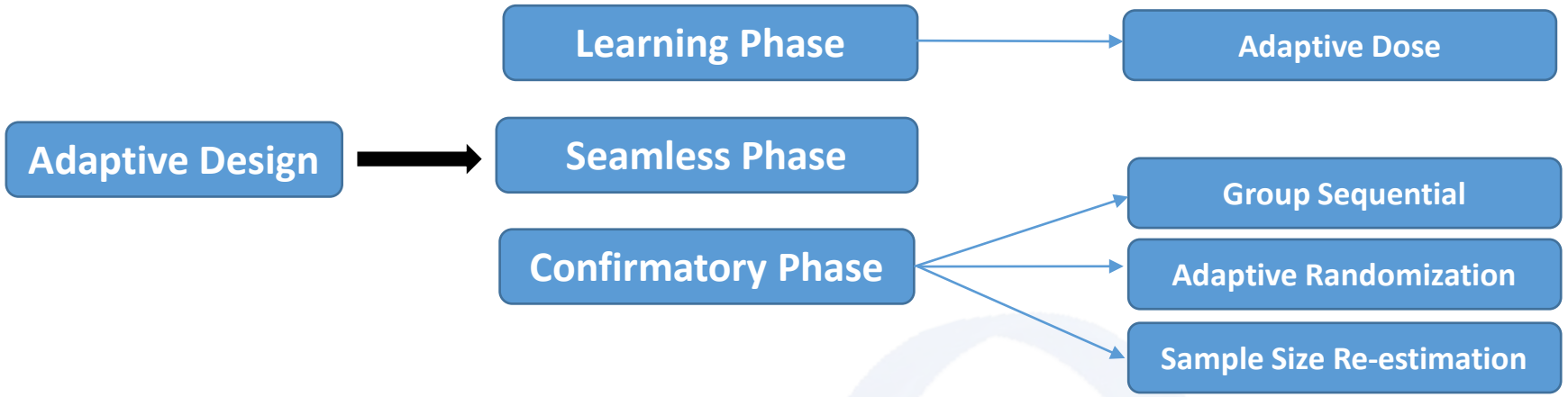






- **Used in Phase 2a for dosing ranging study to inform Phase 2b treatment in PH-PF subjects**
- **Study accepted by FDA based on clinical experience and outcome as measured and visualized through FRI**

Phase 2b/3; Adaptive Study Designs



Adaptive Study Designs in PAH Drug Development Studies

- A Phase 3 Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients With PH Due to COPD

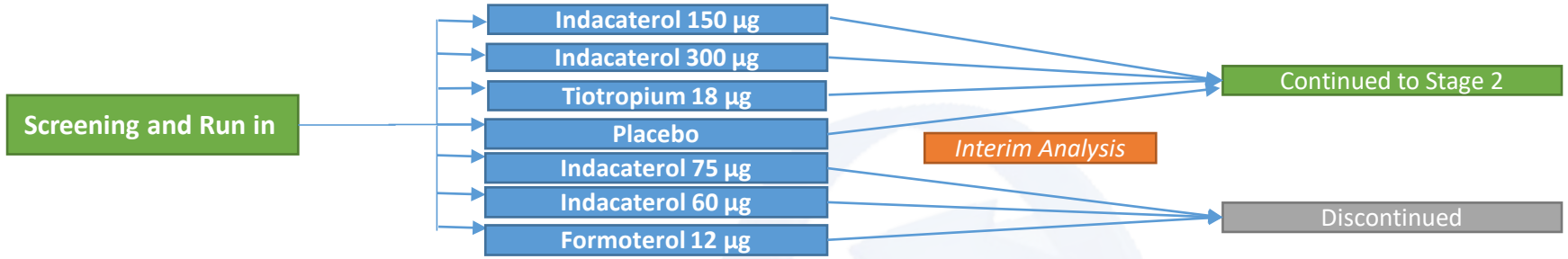
FDA: Guidanhttps://clinicaltrials.gov/ct2/show/study/NCT03496623ce for Industry- Adaptive Design Clinical Trials for Drugs and Biologics

https://clinicaltrials.gov/ct2/show/study/NCT03496623

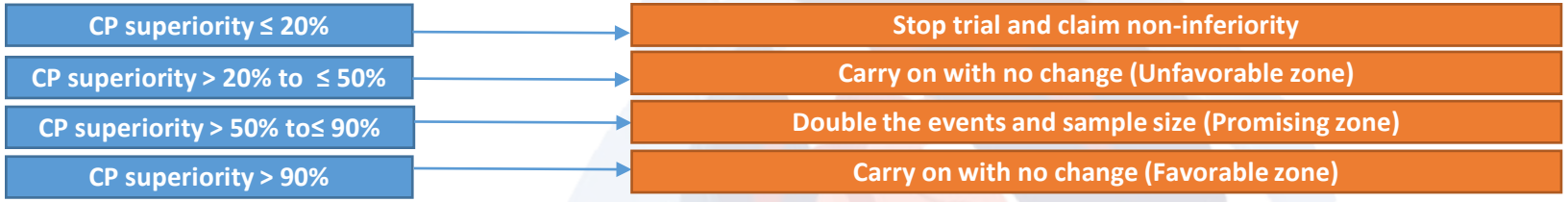
Kairalla, J. A., Coffey, C. S., Thomann, M. A., & Muller, K. E. (2012). Adaptive trial designs: a review of barriers and opportunities. *Trials*, *13*(1), 145.

Experiences, successes, failures to date:
Non-PH development studies

- INHANCE trial : An Adaptive Confirmatory Study for COPD with Dose Selection of Indacaterol at Interim



- EXAMIN trial: The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care



- THE CHAMPION PHOENIX TRIAL : A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention
- ASTIN study : Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke

Clinical Trials.gov : https://clinicaltrials.gov/ct2/show/results/NCT00463567
Bhatt, D. L., & Mehta, C. (2016). Adaptive designs for clinical trials. *New England Journal of Medicine*, *375*(1), 65-74
Krams, M., Lees, K. R., Hacke, W., Grieve, A. P., Orgogozo, J. M., & Ford, G. A. (2003). Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke*, *34*(11), 2543-2548..

Strengths

- More efficiently provides the same information
  - Saves time, money and resources
- Increases the likelihood of success on the study objective by employing SSR (Sample Size Reassessment)
- Yields improved understanding of the treatment's effect
  - e.g., better estimates of the dose-response relationship
- Ethical viewpoint
  - Safeguard patients from unsafe/ineffective treatments at the earliest

Limitations

- Logistically complicated
- Operational Bias
- Statistical Bias
  - Bias associated with the Multiplicity of Options

FDA: Guidanhttps://clinicaltrials.gov/ct2/show/study/NCT03496623ce for Industry- Adaptive Design Clinical Trials for Drugs and Biologics

Support:

- FDA's Guidance for Industry- Adaptive Design Clinical Trials for Drugs and Biologics (February 2010)
- FDA's Guidance for Industry and Food and Drug Administration Staff – Adaptive Designs for Medical Device Clinical Studies (July 2016)
- FDA's pilot program -Promoting the Use of Complex Innovative Designs in Clinical Trials (March 2018)

Future:

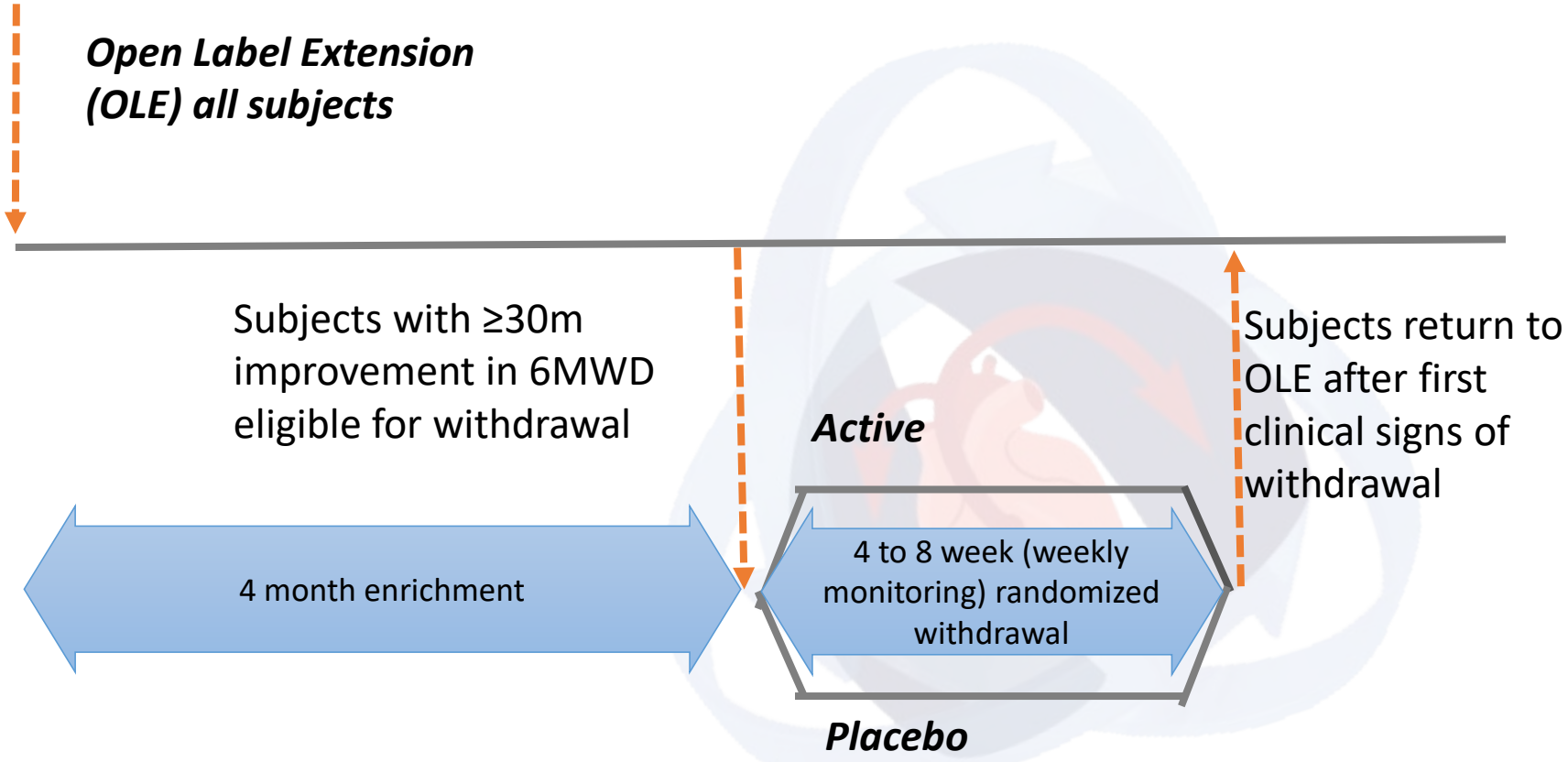
- Complex Innovative Designs

  - Complex Adaptive Designs (Adaptations on multiple factors / may require simulations to determine operating characteristics)
  - Use of external data (Rare diseases)
  - Sharing of control arms across various protocols

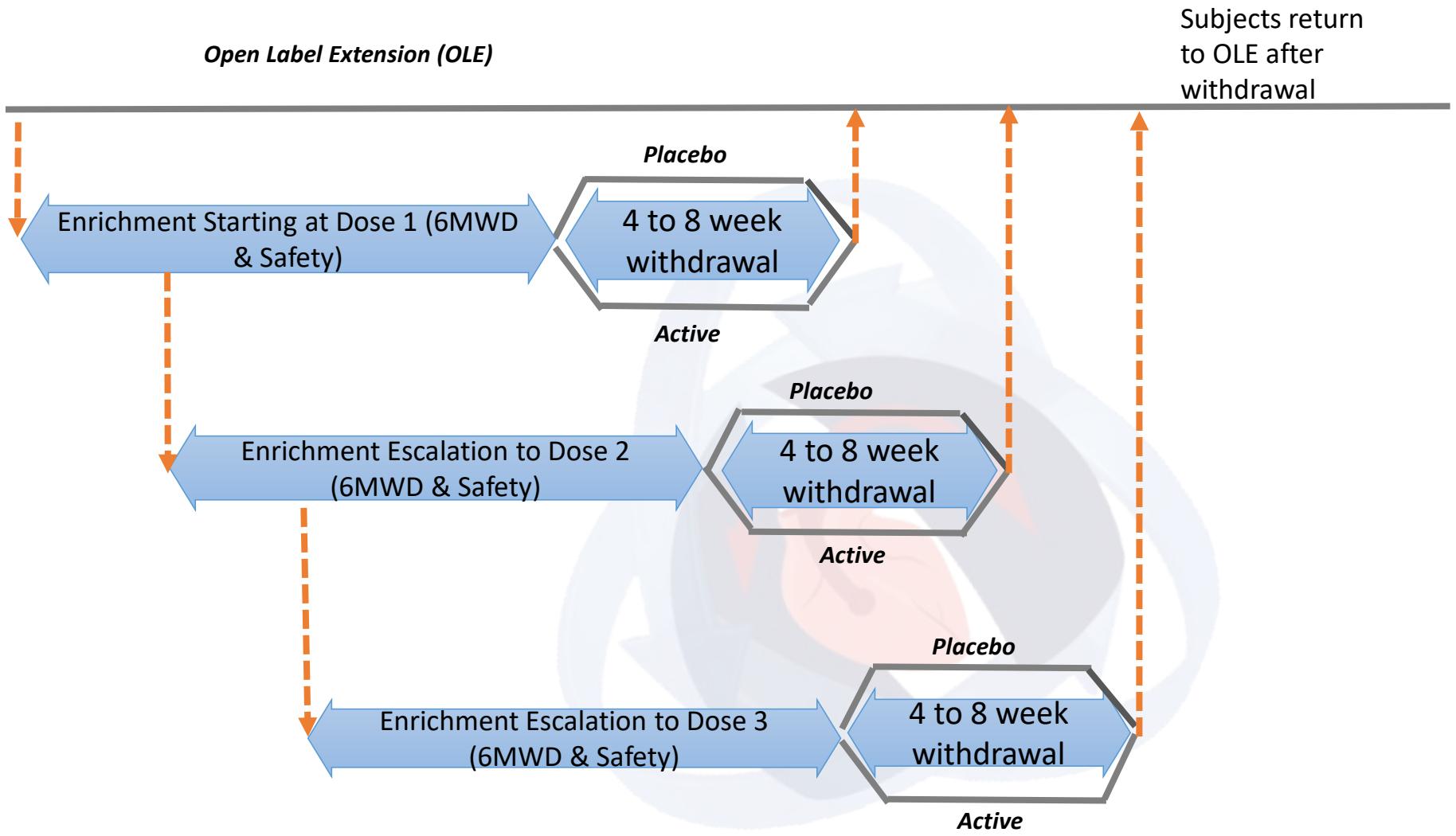
http://www.appliedclinicaltrialsonline.com/fda-advances-innovative-clinical-trial-designs
https://www.fda.gov/downloads/Drugs/NewsEvents/UCM601630.pdf

Randomized Withdrawal Studies (RWS) – Example

Discuss US/OUS Regulatory Acceptance - Status



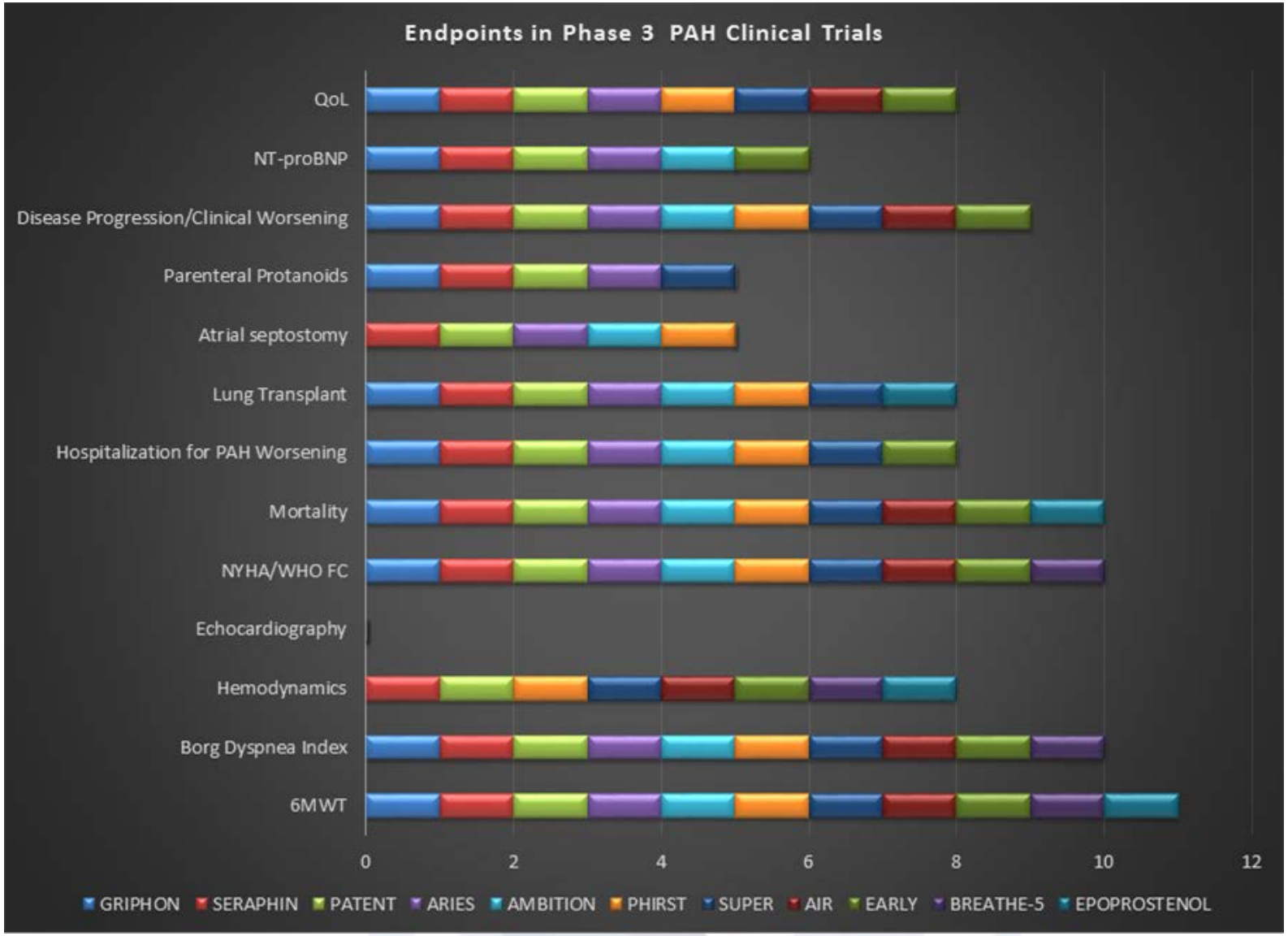
Dose Range Adaptive Withdrawal Study (DRAW) – Early CONCEPT for Discussion



Creating a database covering all 14 PAH approved therapies

Can we generate a tool for testing the hypothesis for innovative endpoints ?

- Has this or can this be developed in collaboration with FDA, Academia and Pharma?
  - **To develop for PAH a database of 14 PAH treatment options approved by the FDA / EMA**
    - **Will provide Insight into defining characteristics and attributes of the disease**
      - **Such as progression, severity, risk factors and correlation to relevant biomarkers, clinically meaningful endpoints and Patient Reported Outcomes (from a collection of primary, secondary and exploratory endpoint data).**
    - **Will allow informed treatment choices and that support regulatory decisions**
    - **We will solicit your thoughts on next steps and potential requirements**
  - **Inputs from the Endpoint Think Tank will be critical in defining the key questions and gaps in our current understanding.**
    - **Define the "scope of the database" that will best provide the answers on short and long term exposure data.**
    - **Collaborative efforts to include other PVRI task force participation including Pediatric and Imaging Task Force members**



Databases: A sample database of what FDA has generated with placebo-controlled trials of 9 approved drugs with PVR, 6MWT (FDA has another smaller database with NT-proBNP). Steve Kawat has a similar database. The Figure below shows endpoints collected in 11 Phase 3 trials. (e-mail feedback from Christine Garnett, FDA Cardio-Renal Division)

	PVRI Working Group - Efficient PAH Drug Development Status update
Background:	Traditional drug development with large sample sizes with clinical outcome driven endpoints (i.e., M&M or TTCW or 6MWD) are no longer practical for rare diseases like PAH in adult and pediatric 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 optimized and so provide very limited useful information. This translates into clinicians and regulators 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.
Common Goals:	1. To learn from the experience and data generated from the 14 PAH treatment options ? 2. To identify a reliable and practical biomarker to discern efficacy in both adult and pediatric populations for PAH 3. To design suitable clinical trials for establishing efficacy in both adult and pediatric populations for PAH
Key Questions	Can an informed selection of a reliable and less invasive endpoint /biomarker provide evidence of effectiveness for drug treatment? Can efficacy be extrapolated from adults to pediatrics?
Objectives/Project Aim	Develop a disease model for PAH to provide insight into the defining characteristics and attributes of the disease with regards to its progression, severity, risk factors and their correlation to relevant biomarkers and multiple clinically meaningful endpoints (including PRO's) in order to facilitate and inform innovative clinical trial designs, endpoints as well as allow informed treatment choices and decisions.
Method/Approach	• Utilize available database for all PAH related clinical trials submitted to date to elucidate biomarker(s)- clinical outcome relationship to provide evidence of effectiveness from primary, secondary and exploratory endpoints (over 12, 24...and specific focus long term data and outcomes).
Project members	• Regulators • Pharma • Academia
Resources	• PVRI
Timelines	Projected 2 years

Endpoints

Moderator Sylvia Nikkho

How best to develop future endpoints based on current experience:

- Summary of assessment of established and composite endpoints by the Endpoint Think Tank
- Can risk scores be transitioned into future endpoints and what are the requirements?
- Topics for a position paper and who volunteers

Members of the Endpoint Think Tank

4 from Patient Organizations, 13 from Academia, 9 from Industry and 2 members from regulatory agencies

Chairs: Olivier Sitbon and Sylvia Nikkho

Patient organizations		Academia		Industry		Reg.	
Fuertes, Juan	PHA Europe	Benza, Raymond	Pittsburgh, USA	Fernandes, Peter	Bellerophon, USA	Prasad, Krishna	MHRA, UK
Denis, Migd.	Soc Latina	Corris, Paul	Newcastle, UK	Meier, Christian	Bayer, Germany	Garnett, Christine	FDA, US
Brad A. Wong	PH USA	Delcroix, Marion	Leuven, Belgium	Nelsen, Andrew	UT, USA		
Michael Gray	PH USA	Ghofrani, H.Ardeschir	Giessen, Germany	Nikkho, Sylvia	Bayer, Germany		
		Hassoun, Paul	Baltimore, US	Peterson, Bob	Liquidia, USA		
		Humbert, Marc	Paris-Sud , France	Quinn, Deborah	Bellerophon		
		Pepke-Zaba, Joanna	Papworth, UK	Budd, David	GSK		
		Rothman, Alexander	Sheffield, UK	De Backer, Jan	FluidDA		
		Seeger, Werner	Giessen, Germany	Ed Parsley	Arena		
		Simonneau, Gerald	Bicêtre, France				
		Sitbon, Olivier	Bicêtre, France				
		Mardi Gomberg-M.	Falls Church, US				
		Farber, Harrison	Boston, US				

PHARC

Updating clinical endpoint definitions

2013

Paul M. Hassoun[1], Sylvia Nikkho[2], Erika B. Rosenzweig[3], Gail Moreschi[4], John Lawrence[4], John Teeter[5], Christian Meier[2], Ardeshir H. Ghofrani[6], Omar Minai[7], Paula Rinaldi[8], Evangelos Michelakis[9], and Ronald J Oudiz[10]

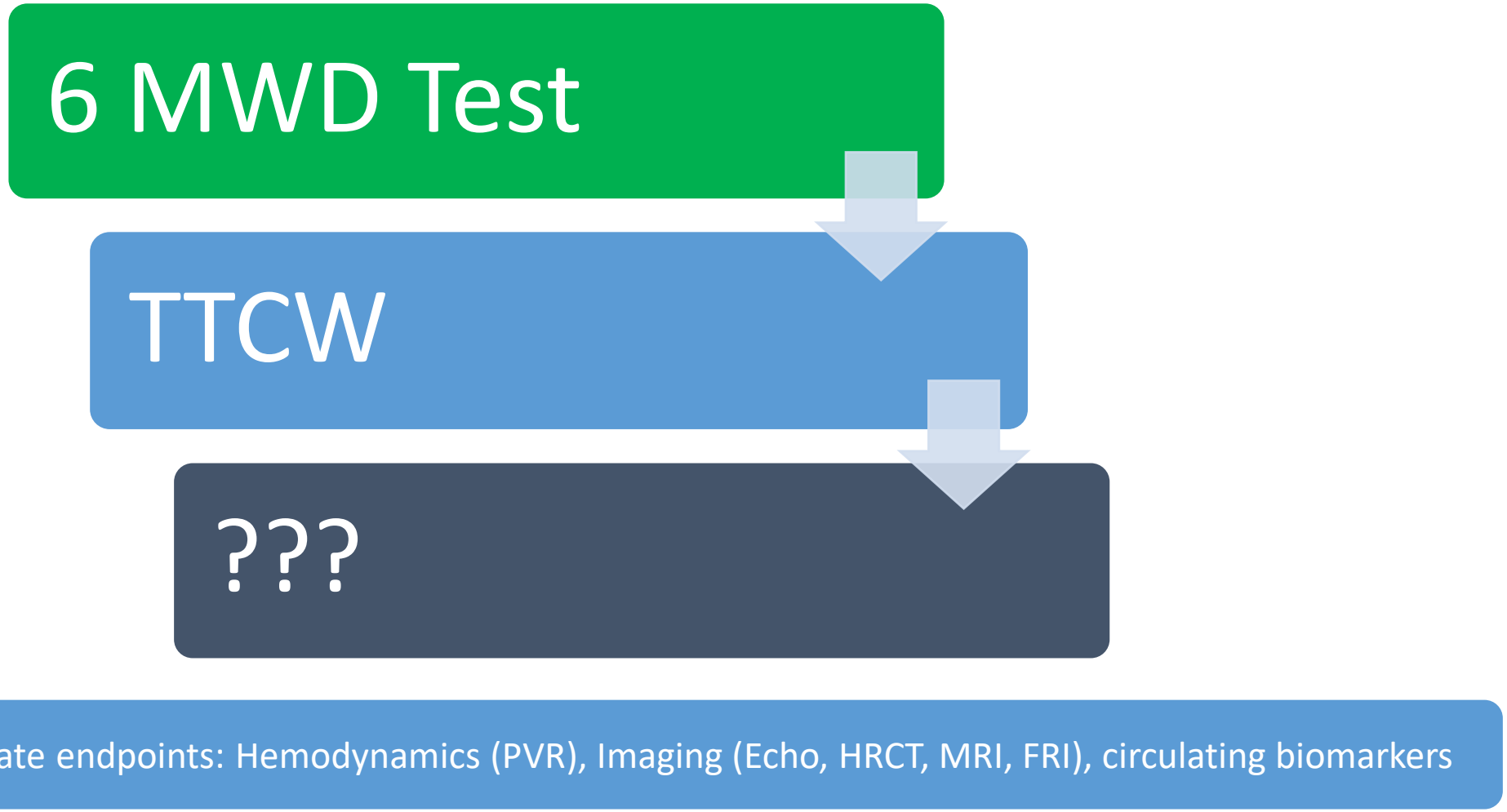
LETTERS TO THE EDITOR

- Letter by Deborah McCollister (Colorado): Clinical trials move away from 6 minute walking distance and a trial duration of only 12 weeks to long lasting TTCW trials.
- 'I can only hope that regulatory agencies, along with the PH physicians and pharmaceutical companies, consider recruitment implications and

keep the best interest of the PH patient in mind when determining the future of drug trial design in this patient population.'

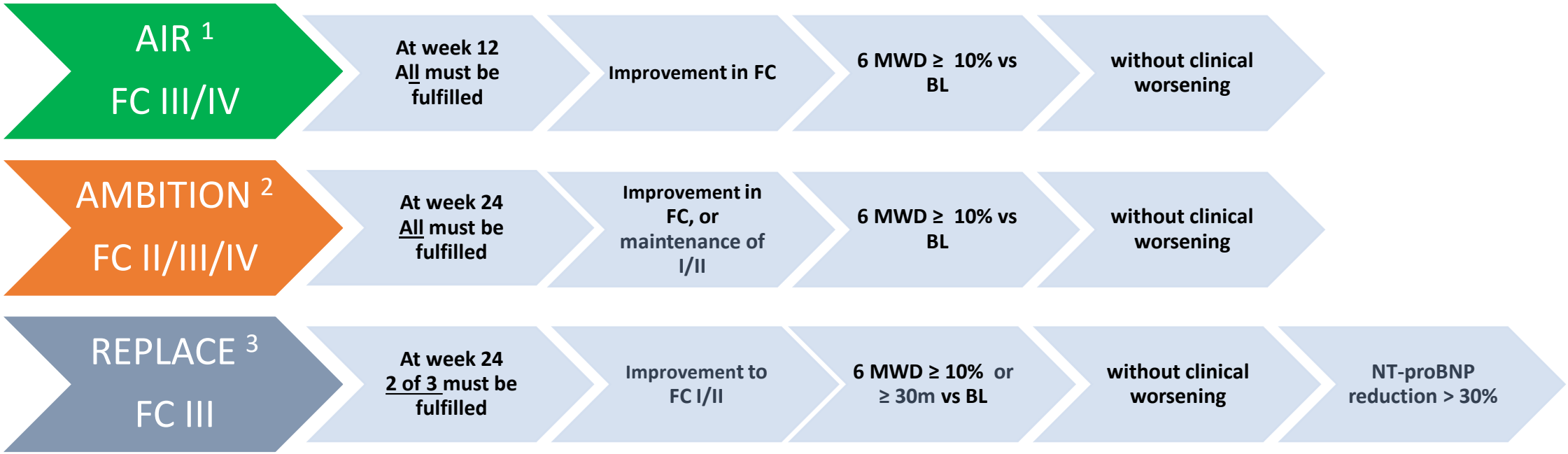
Hassoun PM et al., Pulm Circ 2013;3:206
Hassoun PM, Nikkho S, Oudiz; Pulm Circ 2013
Nikkho S, PVRI Presentation 2012

Evolution of established endpoints over more than 30 years



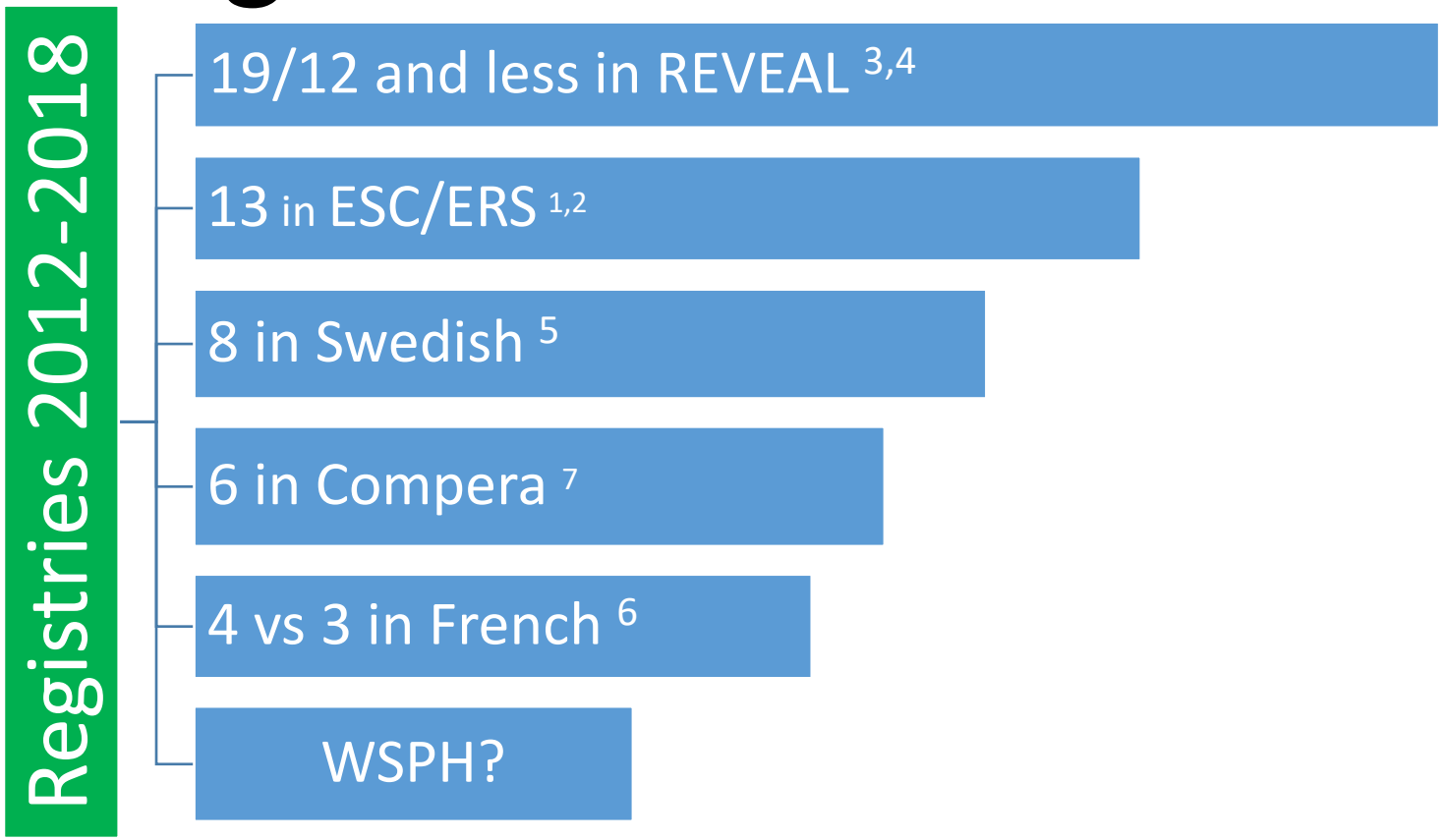
Evolution of Satisfactory Clinical Response (CSR) Endpoints

based on clinical trials



1) Olschewski H, et al., N Engl J Med. 2002 Aug 1;347(5):322-9,
2) Galiè N, et al. N Engl J Med 2015;373:834–844,
3) REPLACE: https://clinicaltrials.gov/ct2/show/NCT02891850

Evolution of 6 risk scores over 6 years aiming at less variables and strata

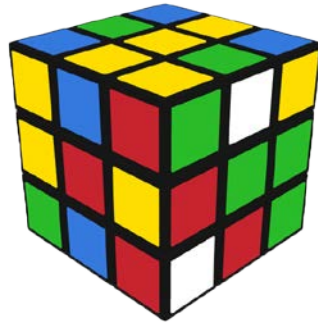


1) Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension… . Eur Heart J 2016; 37: 67–119.
2) Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension… Eur Respir J 2015; 46: 903–975
3) Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator …. Chest 2012; 141: 354–362.
4) Benza RL, Miller DP, Foreman AJ, et al. Prognostic implications of serial risk score assessments …. J Heart Lung Transplant 2015; 34: 356–361
5) Kylhammar D, Kjellstro B, Hjalmarsson C et al., A comprehensive risk stratification … European Heart Journal (2017) 0, 1–7 doi:10.1093/eurheartj/ehx257)B
6) Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation …. Eur Respir J 2017; 0: 1700889
7) Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension... Eur Respir J 2017; 50: 1700740

Composite endpoints

Recommendation from the Think Tank

Look not only at deterioration, look not only at improvement but look at clinical net benefit



Satisfactory Clinical Response	• **Clinical trials:** AIR, AMBITION, REPLACE up to 24 weeks • Components: 6 MWD, FC and new NT-pro BNP without deterioration • Limitation: Low responder rate
Risk Scores	• **Registries (natural history):** Over 6 years 6 risk scores with 19 – 3 criteria • Three main prognostic relevant non-inv. low risk criteria: 6 MWD, FC and NT-pro BNP • Limitation: Low proportion of patients achieving low risk criteria
Future endpoint	• **Goal:** Predictive, non-invasive, feasible with regard to trial size and trial duration • Select the right predictive components • Develop a **clinical net benefit endpoint** • Validation needed as well as agreement by regulators and HTAs

Next Steps of the PVRI Endpoint Think Tank

Dates in 2018	Type of meeting
July 9th , 2018	Face-to-Face meeting for those who attend the PVRI Drug & Discovery meeting in Washington
July t.b.d., 2018	Telephone Conference with a de-briefing from the Washington meeting
Sep 19th t.b.d.	Face-to-Face meeting for those who attend the ERS meeting
13th PVRI Annual World Congress	Presentation of endpoint work

PVRI Innovative Drug Development Working Group – Needs Your Support!

The mission is to create and provide a platform for early and continuous dialogue on innovative clinical and regulatory development strategies where there is free and open discussion between Academics, Patients, Pharma and Regulators Worldwide. We need your support to gather the relevant information and organize workshops with Pharma, Academic and Regulators to discuss and advance our mission and initiatives we've addressed today.

Please complete the information below to provide feedback on your interests so that we can get you involved!

First Name: _____ Last Name: _____

Email Address: _____

Country: _____

Affiliation – Select one and fill in name of Company/Institution

☐ Pharma: _____
☐ Academic: _____
☐ Regulator: _____
☐ Patient Advocacy: _____

Initiative 1: Harmonize Inovative Approaches Through Clinical Trial Designs and Endpoints

Clinical Trial Designs

☐ 2 a/b; FRI-Imaging as a concept for "POC & Dose Ranging"
☐ Phase 2b/3; Adaptive Study Designs, experiences, successes, failures to date with PH development studies and non-PH development studies.
☐ Phase 3; Randomized Withdrawal Studies (RWS) for Phase 3 registration and Concept for Dose-Ranging-Adaptive-Withdrawal (DRAW) Studies.
☐ Creating a database covering all 14 PAH approved therapies as a tool for testing the hypothesis for innovative endpoints.

Endpoints

☐ 6MWD
☐ TTCW
☐ Composite endpoints
☐ Symptoms scores, eg. Dyspnea
☐ Patient-centred outcomes (PCOMS)
☐ Echo vs RHC, imaging methods