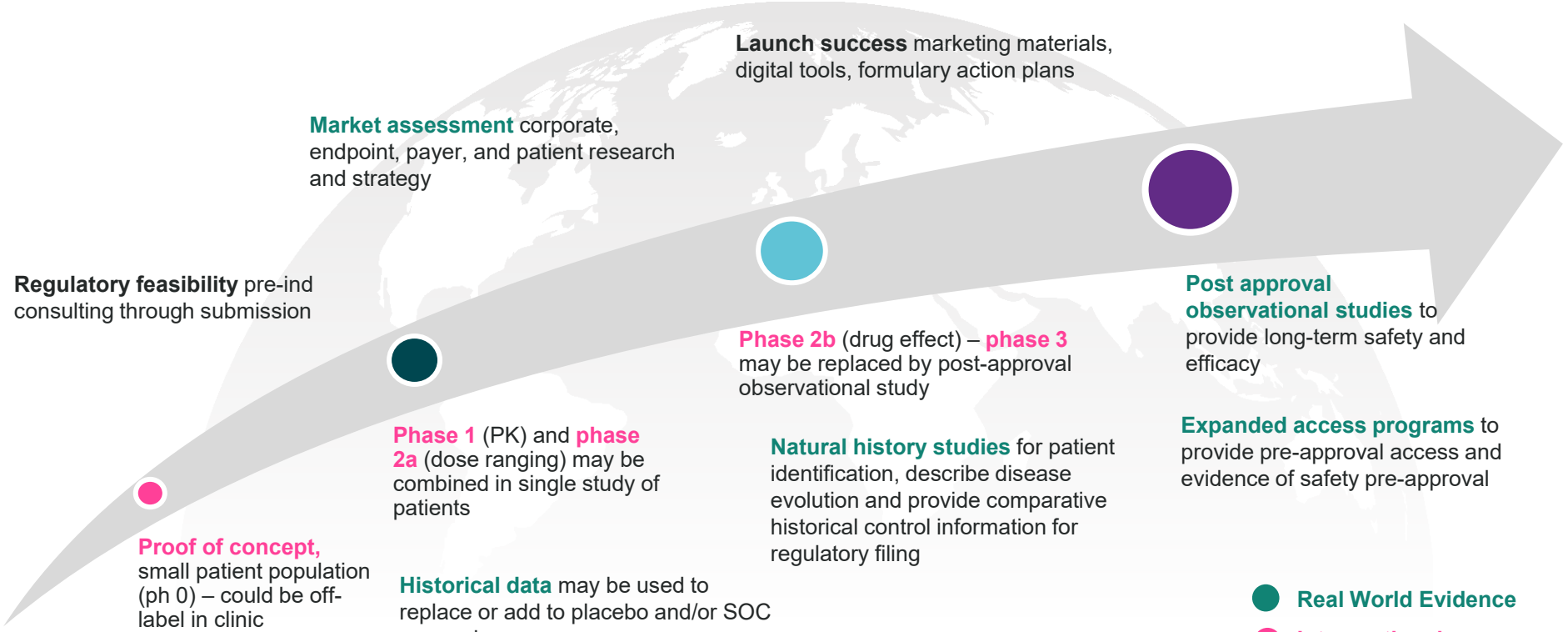
William C. Maier, MPH, PhD (Epidemiology)

VP, Rare Disease, Drug Development Sciences

- 25+ years experience in drug development and commercialisation US, Europe, Asia Pacific– Rare Disease and other therapeutic areas
- Head, ICON (CRO) Centre for Rare Disease – Cross functonal team of internal experts to improve drug development in rare disease
- Expertise in study design, late phase drug development – US, Europe, Japan
- Member Royal Society of Medicine (UK), Member EMA Pharmacoepidemiology Centre of Excellence (ENCEPP)

Orphan drug clinical development – a different pathway



Launch success marketing materials, digital tools, formulary action plans

Market assessment corporate, endpoint, payer, and patient research and strategy

Regulatory feasibility pre-ind consulting through submission

Post approval observational studies to provide long-term safety and efficacy

Phase 2b (drug effect) – **phase 3** may be replaced by post-approval observational study

Phase 1 (PK) and **phase 2a** (dose ranging) may be combined in single study of patients

Natural history studies for patient identification, describe disease evolution and provide comparative historical control information for regulatory filing

Expanded access programs to provide pre-approval access and evidence of safety pre-approval

Proof of concept, small patient population (ph 0) – could be off-label in clinic

Historical data may be used to replace or add to placebo and/or SOC comparison arms.

Real World Evidence

Interventional

Example: Natural History of Perinatal and Infantile Hypophosphatasia: A Retrospective Study – Patient Characteristics

- Report clinical characteristics and medical history data obtained retrospectively for a large cohort of pediatric patients with perinatal and infantile hypophosphatasia.
- Medical records from academic medical centers known to diagnose and/or treat hypophosphatasia were reviewed. Patients born between 1970 and 2011 with hypophosphatasia
- Forty-eight patients represented 12 study sites in 7 countries (including USA); 13 patients were alive, and 35 were dead (including 1 stillborn).
- https://doi.org/10.1016/j.jpeds.2019.01.049

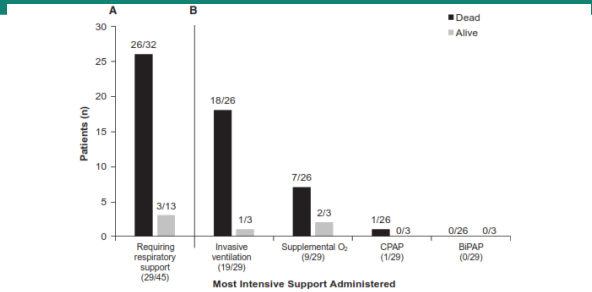
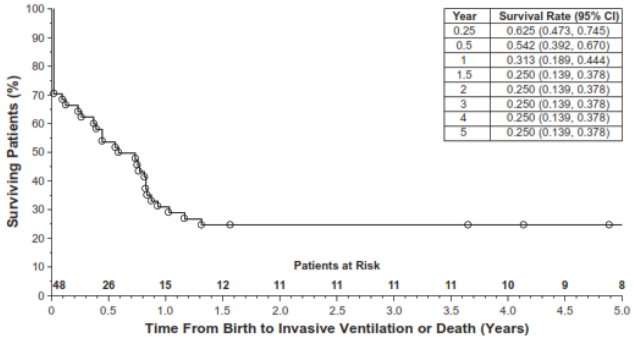


Figure 2. Respiratory support administration. **A,** Distribution of living and dead patients who had required respiratory support. **B,** Greatest required support stratified by type and number of patients alive vs dead at data collection. Values along the x-axis represent the total number of patients (dead and alive combined) who received the specific type of support compared with the total number of patients for whom data were available. *BiPAP*, bilevel positive airway pressure; *CPAP*, continuous positive airway pressure.

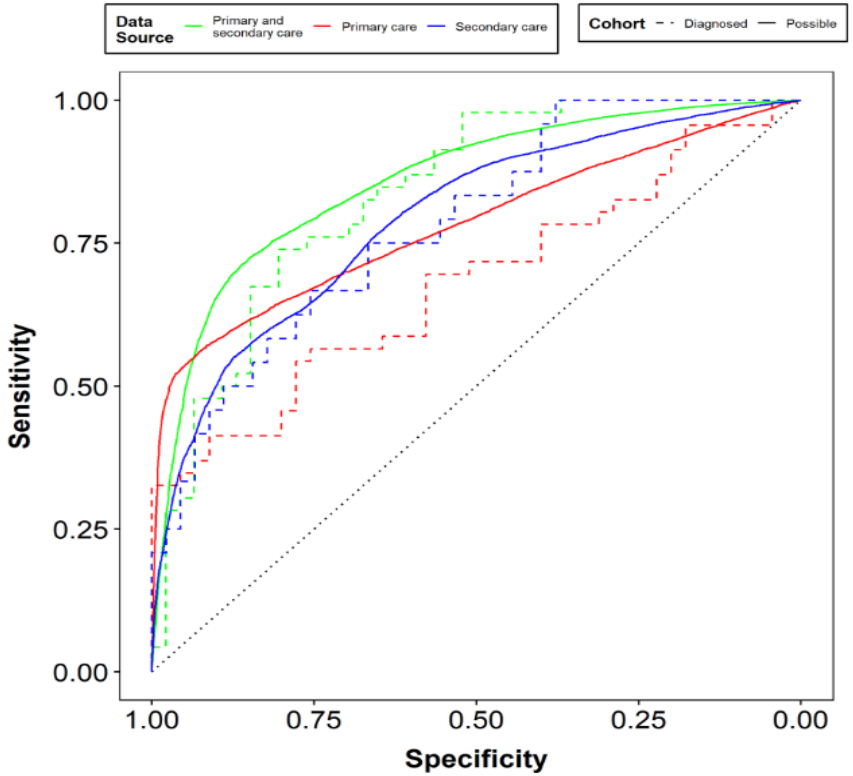


Year	Survival Rate (95% CI)
0.25	0.625 (0.473, 0.745)
0.5	0.542 (0.392, 0.670)
1	0.313 (0.189, 0.444)
1.5	0.250 (0.139, 0.378)
2	0.250 (0.139, 0.378)
3	0.250 (0.139, 0.378)
4	0.250 (0.139, 0.378)
5	0.250 (0.139, 0.378)

Figure 3. Kaplan–Meier plot of time from birth during which patients were not mechanically ventilated by intubation or tracheostomy; 36 patients had an event of invasive ventilation or death, and 12 were censored. *Inset:* cumulative probability of invasive ventilation-free survival.

Example: Detecting transthyretin amyloid cardiomyopathy (ATTR- CM) using machine learning: an evaluation of the performance of an algorithm in a UK setting

- The aim of this study was to evaluate the potential real- world application of a machine learning developed and trained on heart failure (HF) cohorts in the USA, to detect patients with undiagnosed wild type cardiac amyloidosis (ATTRwt) in the UK.
- Clinical Practice GP Data used to identify patients diagnosed with HF between 2009 and 2018 in the UK. International Classification of Diseases (ICD)- 10 clinical modification codes were matched diagnosis codes used in the UK. In the absence of specific codes for ATTRwt, two proxy case definitions (definitive and possible cases) based on the degree of confidence that the contributing codes defined true ATTRwt cases were created using ML
- Algorithm performance was evaluated primarily using the area under the receiver operating curve (AUROC), by comparing the actual versus algorithm predicted case definitions at varying sensitivities and specificities.
- The algorithm performed well in a UK setting using UK data, although performance was poorer than that achieved using US claims data from IQVIA and Optum EHRs. AUROCs of 0.84 and 0.86 were achieved for primary care and linked secondary care records for definitive and possible cohorts, respectively.
- bmjopen-2022-070028.pdf (nih.gov)



Example: international paroxysmal nocturnal hemoglobinuria (PNH) disease registry to product registry

Objective: Evaluate the natural history of untreated PNH and the optimal management of patients, document clinical symptoms/outcomes to elucidate disease progression and variability around the globe, and show long-term safety and effectiveness of eculizumab and the effect of eculizumab on pregnancy outcomes

557 sites

36 countries

4475 patients

Challenges

- Start up challenges
  - Identification of untreated patients
  - Site selection critical; feasibility beneficial to identify level of data available
- Site challenges
  - Decrease site burden with intuitive CRF
- Working with multiple sponsors to design base registry

Results

- Registry provided first information to compare how disease changed over time across multiple geographies and different age groups
- Information on sponsor product was used to expand the product label to patients without transfusions (EMA, 2016)https://www.ema.europa.eu/en/documents/presentation/presentation-pnh-indication-update-based-data-global-registrymartine-zimmermann_en.pdf
- Label change to use in pregnancy. Eculizumab in Pregnant Patients with Paroxysmal Nocturnal Hemoglobinuria | NEJM

Example: FDA drug approval using external control information derived from a patient registry

April 2017

FDA approves first treatment for a form of Batten disease | FDA

Background

- External control information from an ongoing patient registry was used in the approval of Brineura® (cerliponase alfa), the enzyme replacement therapy that helps treat CLN2 disease, a common form of Batten disease
- **Historical control population based on patients with CLN2 in the DEM-CHILD database with collected clinical information from records and patient interviews**
- Several differences in the historical population relative to the trial population including different distributions of age, genotype and gender
- Efficacy - clinical rating scale developed specifically for CLN2 patients
  - Only two domains (Motor and Language) were measured in the historical cohort
  - FDA felt Language domain not measured same as in trial – Focus only on Motor Domain
- **In the best match analysis patients were matched by baseline motor score, baseline age and genotype (genotype categories were defined as 0, 1 or 2 key mutations)**
  - 17 best matches were identified using this approach
- According to this analysis there was a progressively larger difference with time, between the treated and historical groups 18%, 29%, and 59% at 48, 72 and 96 weeks respectively

Example: Phenylketonuria (PKU) EAP & Registry - Data on pre-approval product use

- Design of the regulatory and commercialization strategy for PKU treatment with orphan drug designation and fast-track status
- Study Details | Sapropterin Expanded Access Program | ClinicalTrials.gov
- Example: Nationwide Childrens Hospital Involved In Expanded Access Program for Treatment of PKU
- Expanded access program (EAP) for PKU patients that began at NDA filing
- EAP addressed unmet patient needs
  - Clinical, humanistic & safety data collected pre-approval
  - 42 sites; 400 patients
  - Treated/followed until product approval
- Used as supplemental data in FDA application - CPY Document Title (fda.gov)

ICON Centre for Rare Diseases

We are guided by patients who understand better than anyone else that rare disease alters entire lives. We help sponsors accelerate rare disease drug development and patient access through unrivaled expertise, innovative strategies, and patient partnerships.

Contact the ICON Centre for Rare Diseases Team

iconplc.com