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Cécile Ollivier (COO)

Wearables and Patient Reported Outcomes: new wins?

Disclaimer

- These PowerPoint slides can be shared but source should be acknowledged

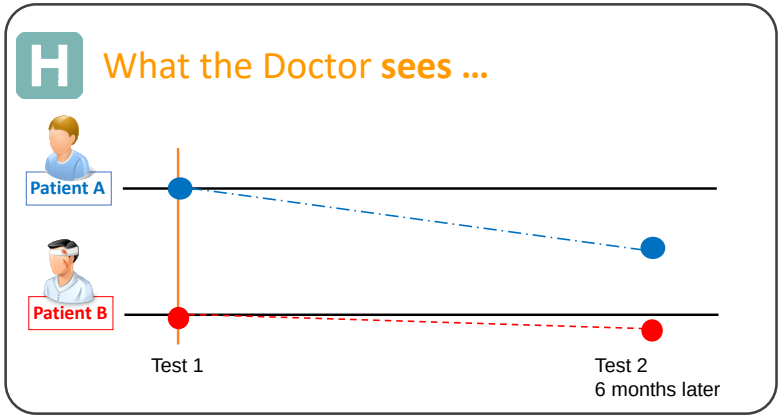
- Views are my own and I am not an oncology expert

- I am a former EMA employee and now an employee of Aparito

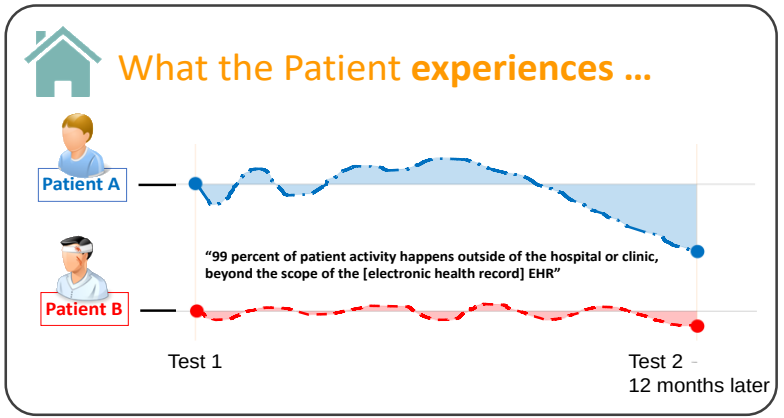
Presentation Overview

- Can digital tools help us address unmet needs ?
- Regulatory points to consider
- PROs and technology

Collecting Patient Data in Clinical Trials



VS



'Episodic snapshots'

Currently: We only see data at clinical visits

Current problems in clinical trials

- Clinical trial complexity
- Participation burden and missed engagement
- Cost
- Clinical capacity

'Disease in motion'

The future: Monitoring patients at home 24/7/365

Benefits

- Patient Centric
- Cost reduction
- Better patient centric study design
- Improved patient access to studies, incl. diverse population
- Rapid recruitment and improved retention (30% per study)

https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development
S. Elvidge, "Importance of Patient Retention Strategies," Life Science Leader

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Transitioning Landscape

1

2

3

Crawl....
Traditional approach

Pharma continues it's current approach to clinical trials, using clinical sites and capturing data using paper and pens.

Walk...
Hybrid Model

Companies will leverage technology to gather data. The market adoption however won't be huge. This will take time resulting in a hospital and tech clinical trial model.

Run...
Virtual Model

Companies will have adopted technology and virtual clinical trials as a standard way of conducting trials. They will also leverage the huge data set generated to find insights using AI.

Healthcare Trends

- ePatient
- More engaged participants with increased expectations
- Digital health has become a thing
- Cheaper technology
- IoT's
- Precision medicine

Barriers to Entry

- Expert regulatory knowledge
- Expert technologists in the Clinical Trial space
- Clinical trial expertise
- Commercial expertise in the Pharma sector

Can digital tools help us address unmet needs ?

Paediatric PAH example

What are the hurdles?

Clinical and pharmacological hurdles

- Population: rare and heterogeneous
- Gaps in knowledge: pathophysiology, extrapolation, endpoints
- Medicinal products: high number of competing products
- Treatment strategies: from monotherapy to combinations
- Off-label use

What are the hurdles?

Local differences preventing to conduct multiregional paediatric drug development

- Regulatory requirements *(EMA PIPs and FDA written requests)*
- Operational practicalities *(standards of care, cultural expectations)*
- Patients and families do not want to enrol in any clinical trials *(endpoints, burden of CTs)*

Regulator's duty to ensure that medicines for use in children are of high quality, ethically researched and authorised appropriately

- Such an assessment requires clinically robust and relevant data

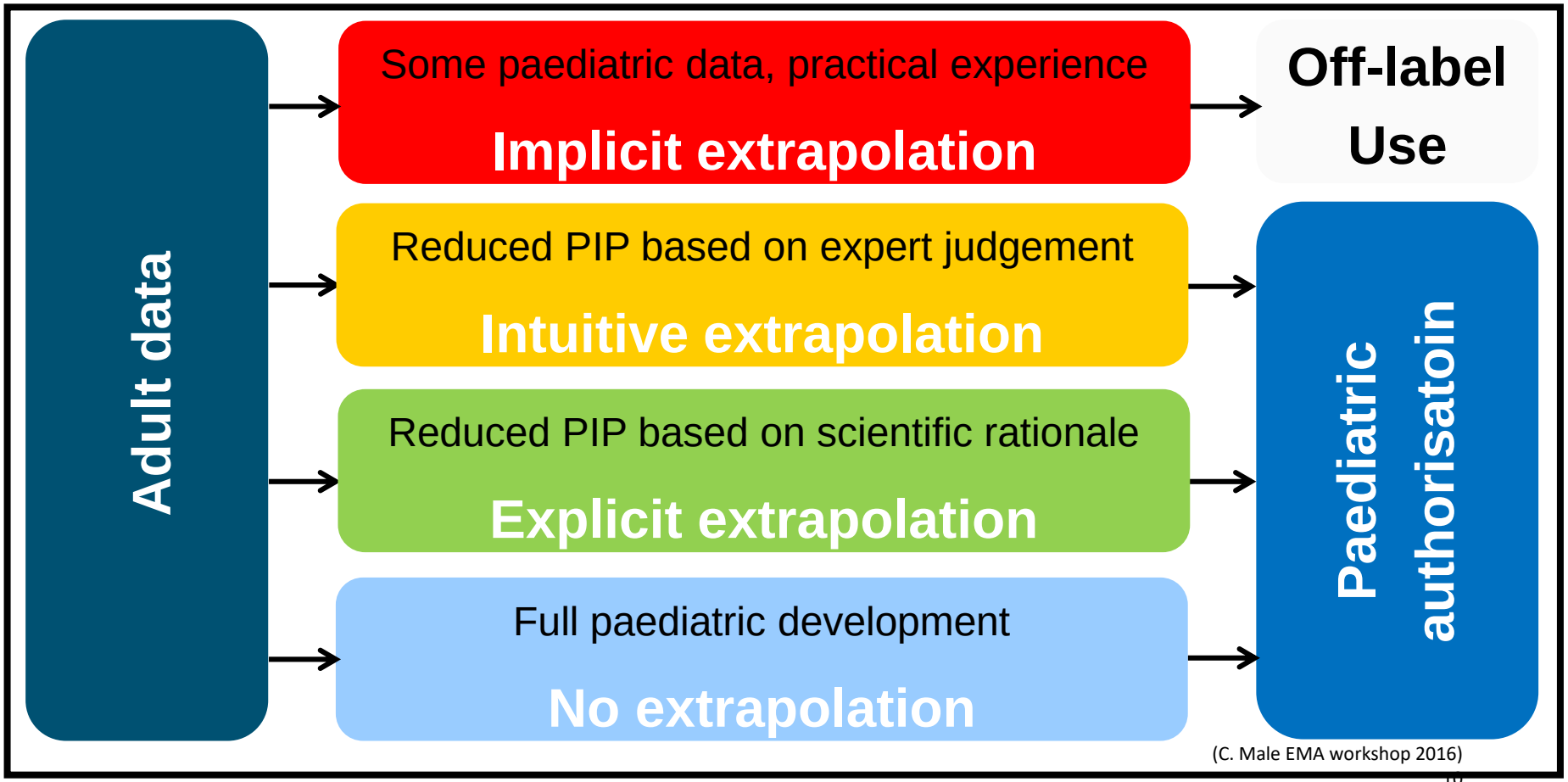
Paediatric PAH – Paediatric Investigation Plan overview (June 2017)

Class of products	Product	PIP	WR*	Authorisation for adults			Authorisation status for children		
				EU	US	Canada	EU	US	Canada
Prostacyclin Analogue	Treprostinil	X		NO	YES	YES	**NO**	**NO**	**NO**
	Selexipag	X		YES	YES	YES	**NO**	**NO**	**NO**
	Treprostinil diethanolamine	X		NO	YES	NO	**NO**	**NO**	**NO**
	Iloprost	N/A		YES	YES	NO	**NO**	**NO**	**NO**
Endothelin Receptors Antagonist (ERAs)	Bosentan	X		YES	YES	YES	PK data	**NO**	PK data
	Ambrisentan	X		YES	YES	YES	**NO**	**NO**	**NO**
	Macitentan	X	WR*	YES	YES	YES	**NO**	**NO**	**NO**
Phosphodiesterase type 5 inhibitor (PDE5 inhibitor)	Sildenafil	X	WR*	YES	YES	YES	**YES**	**NO**	**NO**
	Tadalafil	X	WR*	YES	YES	YES	**NO**	**NO**	**NO**
Guanylate cyclase (sGC) stimulators	Riociguat	X		YES	YES	YES	**NO**	**NO**	**NO**
Vasodilator	Epoprostenol	N/A		YES (NAP*)	YES	YES	**NO**	**NO**	**NO**

Paediatric PAH global strategies– Ollivier et al, JAHA 2019

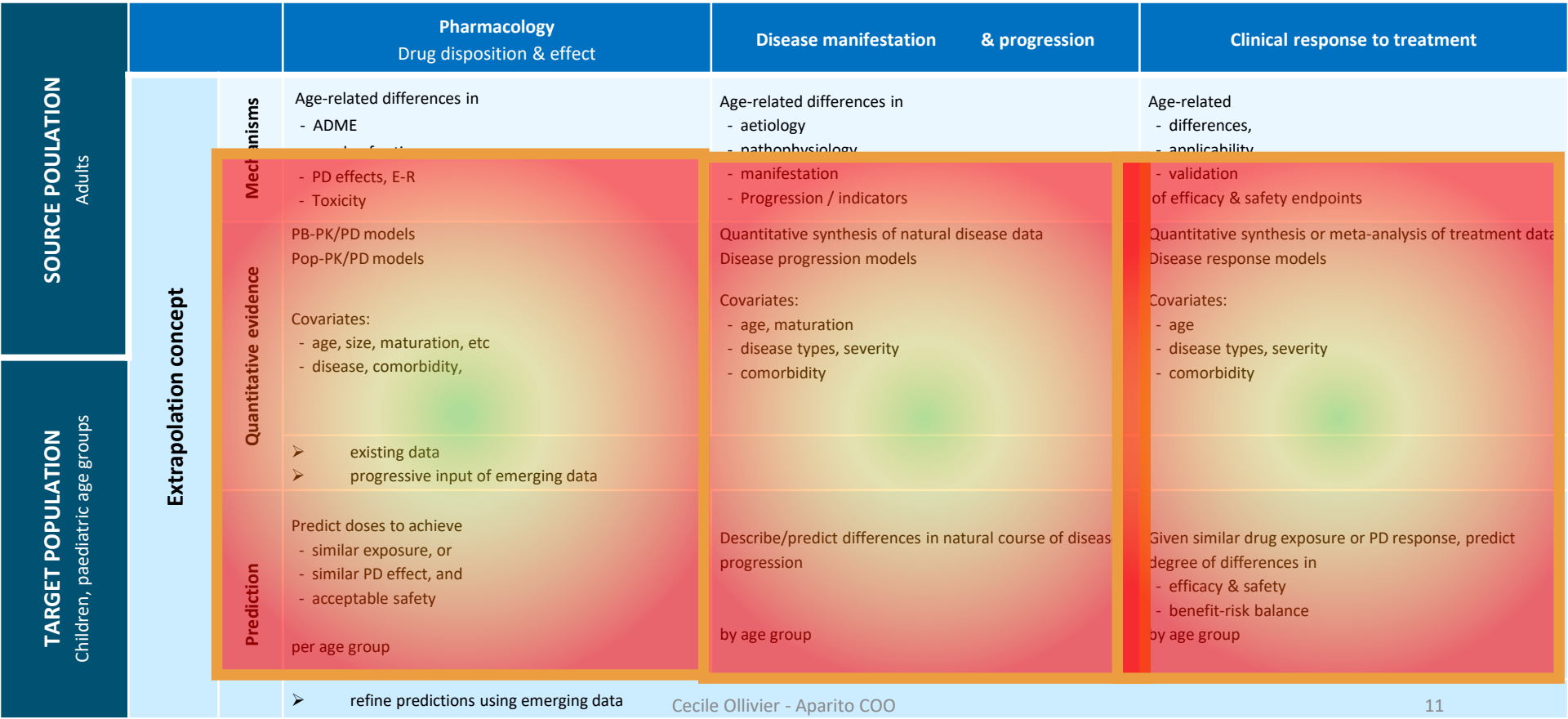
* NAP: Nationally authorised product - *WR written Request

Paediatric indications and off label challenges



(C. Male EMA workshop 2016)

Off-label use data can't lead to licensing*



Example: Pulmonary Arterial Hypertension

- TC with FDA in September 2016: Using the extrapolation framework to structure the discussion allowed to identify that EMA and FDA were much closer than anticipated.

- June 2017: EMA/FDA/HC workshop on paediatric PAH:

Global consensus achieved for extrapolation, study design and endpoints

✓ PK/PD randomised dose controlled studies (vs placebo controlled) - TBD

✓ Moving towards non-invasive echocardiography (instead of RHC)

✓ Moving towards actigraphy instead of 6MWT

✓ PROs and QoL to be developed

Agreed non-invasive EP with potential use in CTs

Table 3.Noninvasive End Points With Potential Use as End Points in Clinical Trials in Children

End Point Modality	Potential Treatment Goals to be Considered	Strengths	Limitations
WHO-FC	WHO-FC improvement	• Convenience • Predictive of transplant-free survival in pediatric PAH	• Variability in classifications among clinicians • Definitions of symptoms may differ and not be reliable in children
NT-proBNP	NT-proBNP lowering	• Simple procedure (plasma) • Likely predictive of transplant-free survival in pediatric PAH prognosis	• Not a specific indicator for PAH only • Impacted by cause of PAH • The normal value of NT-proBNP in children can vary with age
Echocardiography	• TAPSE improvement • 3-Dimensional right ventricular function • Fractional area change	• Widely used for monitoring in patient population • 3-Dimensional echocardiography offers new options with end points	• High operator variability • Likely larger sample size • No consensus on which echocardiographic end point should be used as a primary outcome
Actigraphy Actigraphy	• Physical activity count • Heart rate variability	• Children friendly • Simple and can continuously record physical activity for days and weeks • Correlates with 6MWD Test, mPAP, and PRVi • Sensitive and, thus, potentially requires smaller sample size	• Needs to be validated in an interventional trial • Needs to optimize the cutoff values for different levels of physical activities across different devices • Seasonal and school/holiday influences
PRO PRO	Not studied	Direct measurement of how a patient feels, functions, and survives	Not being developed

Paediatric PAH global strategies– Ollivier et al, JAHA 2019

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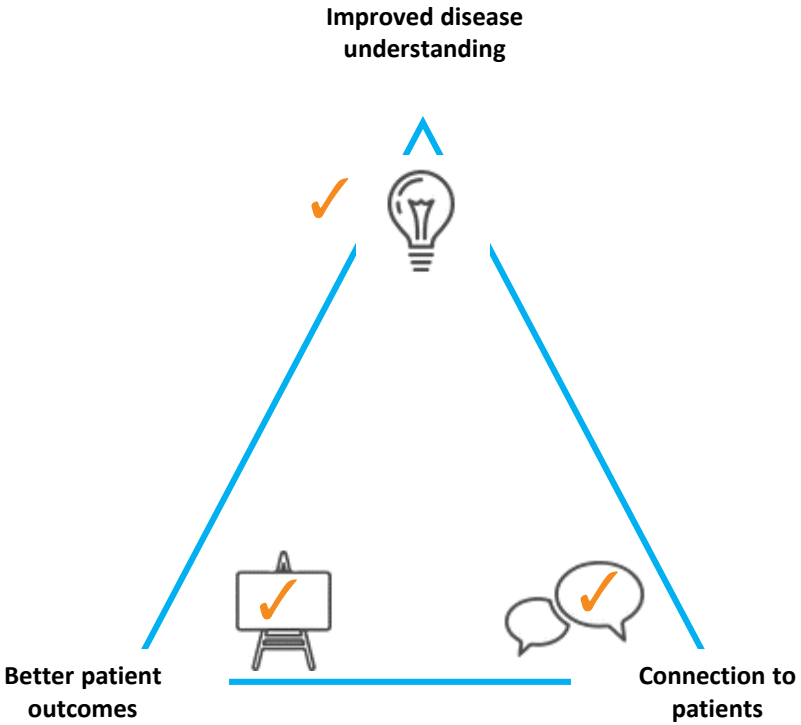
Assessment of physical function in children with cancer: A systematic review Grimshaw, SL, et al. Pediatr Blood Cancer. 2018; 65:e27369

- 101 physical function measures were identified across 154 studies.
- Measurement property data were available for 12 measures.
- Only 2 outcome measures were assessed in more than 1 study.
- Poor methodological quality of the included studies was the main limiting factor.

Conclusions

- There is very limited population specific evidence to guide the selection of physical function measures in children with cancer.
- Further research is needed to provide a basis for more effective clinical assessment and management.

Unique Opportunity with technology



Regulatory points to consider

- Context of use
- Qualification

Context of Use

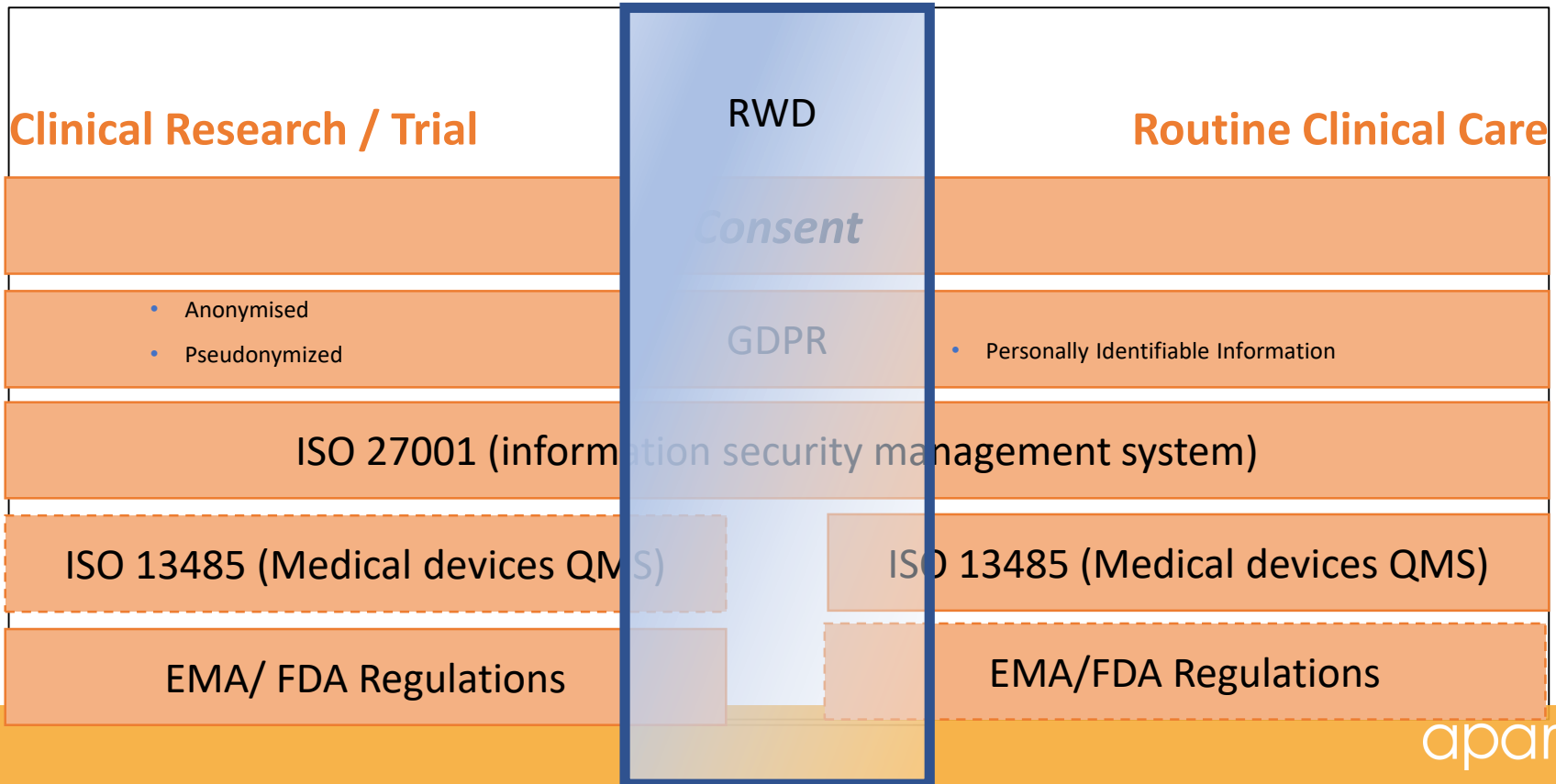
Clinical Research / Trial

Routine Clinical Care

*"Depending on the device and the way it is being used, FDA/ CDRH clearance **may or may not** be needed when the device is used in a clinical trial. (not all cleared devices will be acceptable for use clinical trials and not all devices used in trials with require approval or clearance)"*

Leonard Sacks
Office of Medical Policy
CDER, FDA
February 2019

Context of use challenge



EMA Qualification

- …on the regulatory validity and acceptability of a specific use of a proposed method in R&D context (in non-clinical and clinical studies)

- Voluntary, scientific pathway for innovative methods or drug development tools not yet integrated in the drug development and clinical management paradigm

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

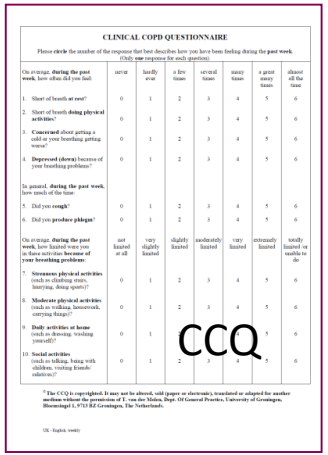
10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Qualification Example – Physical Activity (PA)

- A crucial Patient Reported Outcome (PRO) for COPD
  - As COPD prevalence is increasing, new outcome measures are needed to enhance the understanding of therapeutic interventions
  - For patients (and physicians) PA limitations is a major concern in COPD
  - PA is associated with disease progression, and an important predictor of mortality in COPD
  - There are available measures related to PA, but no targeted measure of all relevant aspects of PA had experience in COPD



Acknowledgement: Solange Rohou

The PROactive consortium

EFPIA members

Chiesi
GlaxoSmithKline
Almirall
AstraZeneca
Boehringer Ingelheim
NOVARTIS
ucb
Pfizer

Funding

- IMI JU funding: € 6.767.597
- EFPIA contribution: € 7.230.350
- Total project cost: € 15.635.822

PROactive

Patient / Scientific organizations

Astma Fonds Binnenkort Longfonds
BRITISH LUNG FOUNDATION
European Respiratory Society

Academic partners

CREAL centre de recerca en epidemiologia ambiental
The University of Edinburgh
Universität Zürich
Royal Brompton & Harefield NHS Foundation Trust

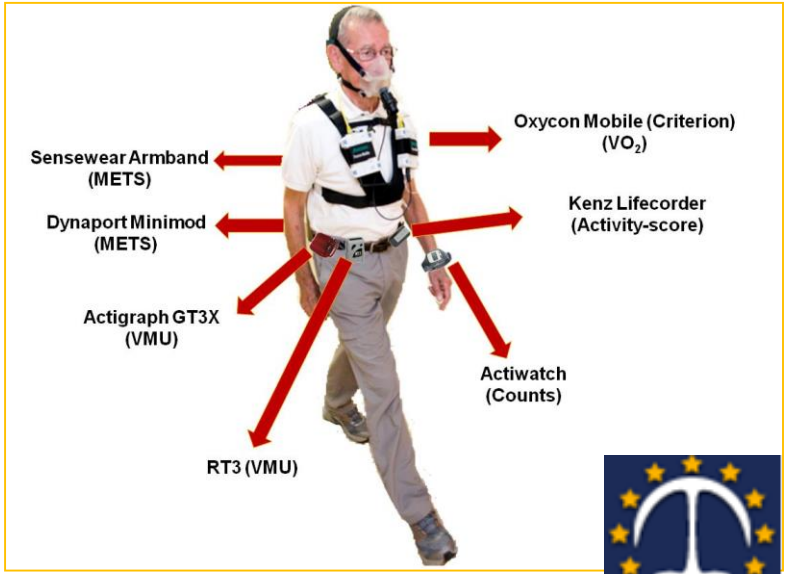
SME

choicepharma realizing visions

Acknowledgement: Solange Rohou

Example: PROactive

- Physical activity is important to monitor patient health status and assess the effect of a treatment
- The PROactive consortium has qualified hybrid PRO tools to assess PA experience of patients with COPD, and able to support medicinal product labelling claims
  - 4 EU languages /cultures /patient populations
- PROactive has paved the way for interventions to enhance patient's physical activity and physical activity experience
- **Multi-stakeholder interactions – a key success factor**



Acknowledgement: Solange Rohou

PROs and technology

“Expectations are growing for PRO results and other clinical outcome data to be incorporated into the benefit risk evaluation of cancer products.”

Source: P. Kluetz, D. O’Connor, K. Soltys - Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada – The Lancet Oncology VOLUME 19, ISSUE 5, PE267-E274, MAY 01, 2018

EMA	FDA
PRO	PRO
health-related quality of life (HRQL)	health-related quality of life (HRQL)
Reflection paper on the use of HRQL in the evaluation of medicinal products 2016 released **“Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man: The use of patient-reported outcome (PRO) measures in oncology”.**	December 2018, the FDA released an update to their guidance “Clinical Trials Endpoints for the Approval of Cancer Drugs and Biologics (QoL, Physical functioning, patient and caregiver experience) Patient Focused Outcome Measurements roadmap FDA guidance on Patient-Focused Drug Development

Gaucher disease example – Can we learn from it?

Orphanet Journal of Rare Diseases

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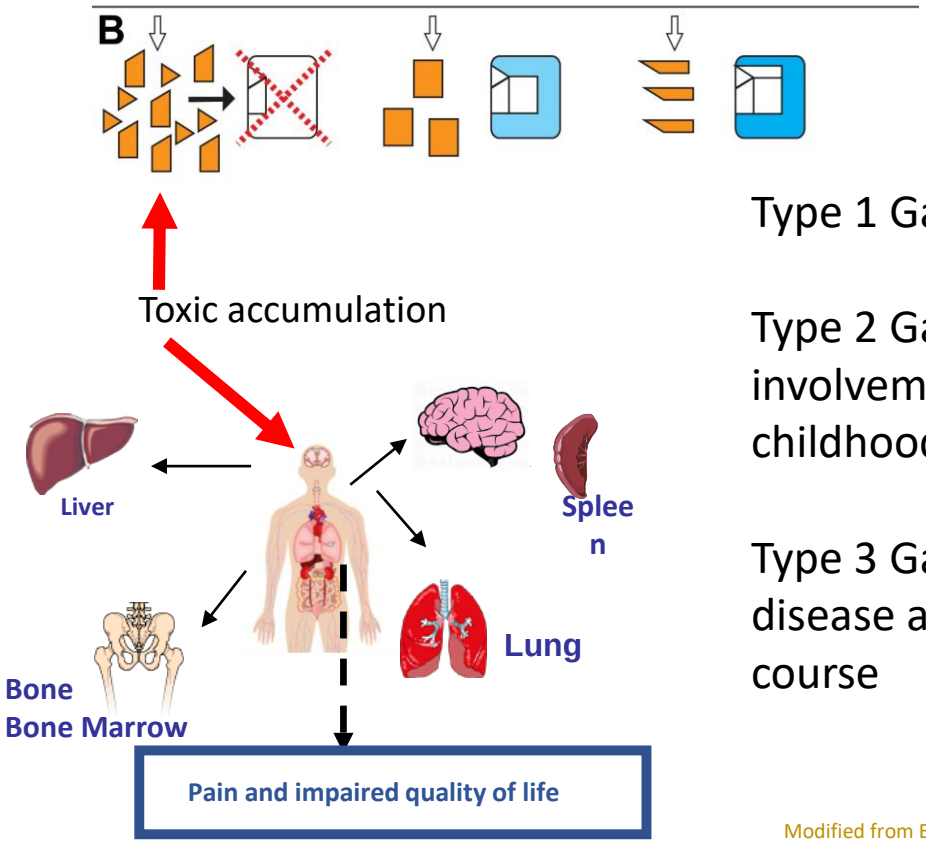
Research | Open Access | Published: 05 September 2019

Measuring disease activity and patient experience remotely using wearable technology and a mobile phone app: outcomes from a pilot study in Gaucher disease

Aimee Donald, Huseyin Cizer, Niamh Finnegan, Tanya Collin-Histed, Derralynn A. Hughes & Elin Haf Davies

Orphanet Journal of Rare Diseases **14**, Article number: 212 (2019) | Download Citation

Gaucher disease



Type 1 Gaucher Disease: no brain involvement

Treatment

Type 2 Gaucher Disease: Very severe brain involvement in infancy – premature death in childhood

Type 3 Gaucher Disease: Both severe body disease and brain disease – variable disease course

Modified from E Beutler and GA Grabowski, *The Metabolic & Molecular Bases of Inherited Disease* 2001

mHealth in Gaucher disease

Methodology

- Baseline gait/ ambulation assessment (6MWT and GAITrite/ Zeno walkway)
- The modified Severity Scoring Tool disease scale
- Wearable device (3D accelerometer)
- PROs
- Events (symptoms)

mHealth in Gaucher disease

Results

- 21 patients enrolled;
  - 5 Type 1 GD age 13 yrs. – 42 yrs. (mean 24.8 yrs)
  - 16 Type 3 (nGD) aged 5 yrs–48yrs. (mean 21yrs).

- The Child Health Utility 9D (CHU9D) showed a statistically significant difference between disease groups, GD Type 3 (Neuronopathic) patients reporting overall lower health-related quality of life.

mHealth in Gaucher disease

Results

- 210 events reported in total

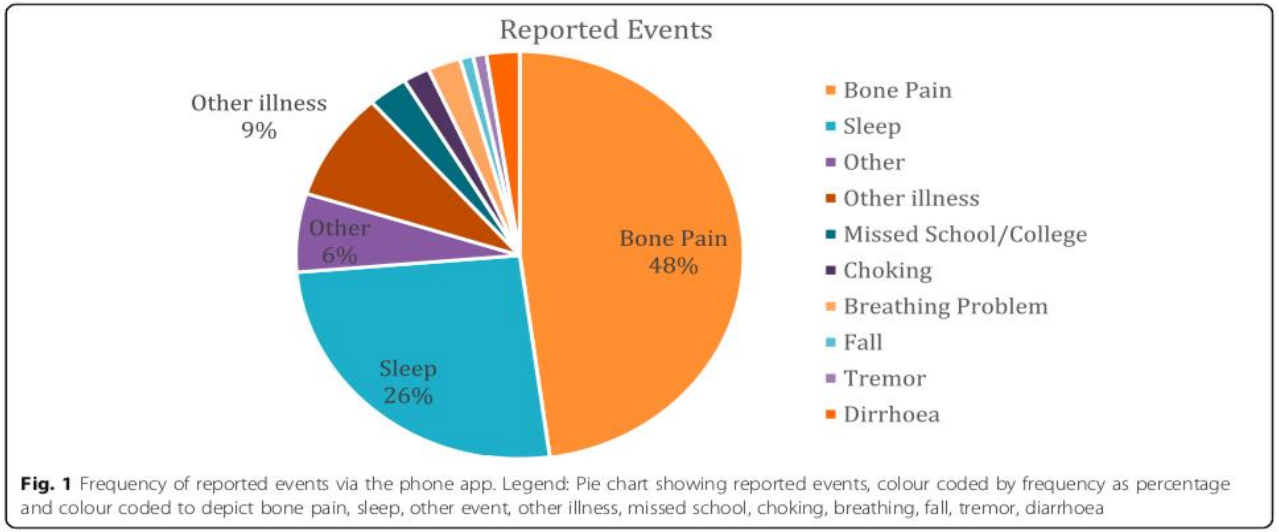


Fig. 1 Frequency of reported events via the phone app. Legend: Pie chart showing reported events, colour coded by frequency as percentage and colour coded to depict bone pain, sleep, other event, other illness, missed school, choking, breathing, fall, tremor, diarrhoea

mHealth in Gaucher disease

Learnings

- Patients capability to cope / easily overwhelmed (esp Type 3 GD).
- Good training and on-going support essential
- Technical failures / damages

Next steps

- Extend to wider population with updates to the technology based on the learnings

Global Disease Registry for neuronopathic Gaucher

Drug Safety
https://doi.org/10.1007/s40264-019-00848-9

ORIGINAL RESEARCH ARTICLE

Check for updates

Patient Registries: An Underused Resource for Medicines Evaluation

Operational proposals for increasing the use of patient registries in regulatory assessments

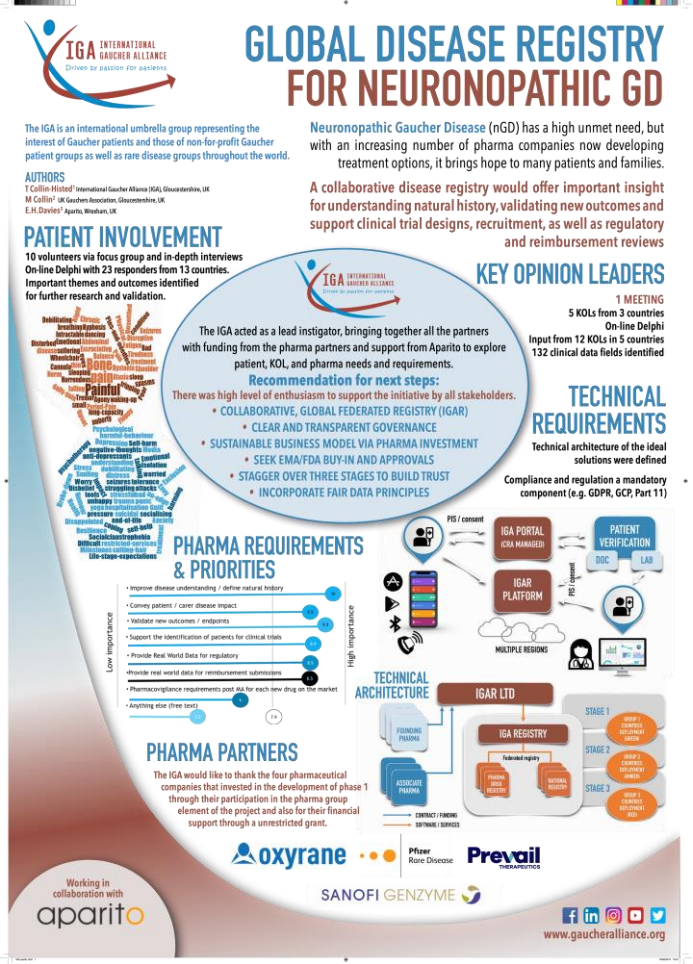
Patricia McGettigan[1] · Carla Alonso Olmo[2] · Kelly Plueschke[2] · Mireia Castillon[2] · Daniel Nogueras Zondag[2] · Priya Bahri[2] · Xavier Kurz[2] · Peter G. M. Mol[3,4]

Global Disease Registry for neuronopathic Gaucher

Co-creation driven by the patient community.
Key areas:

- Understanding natural history
- Validating new outcomes and support clinical trial designs
- Facilitate recruitment
- Generate data for regulatory and reimbursement reviews.

Collin Histed, T et al. EWGGD (2019)



Experience so far

- Very positive feedback from patients, sponsors and HCPs
- Patients and HCPs input is key to success in designing the technology
- Before launching a big scale study, feasibility studies are needed for validity, reliability and allow changes.

Can the Gaucher experience benefit the oncology community?

- These principles applies across populations and therapeutic areas
- Electronic data capture or electronic patient reported outcomes (ePRO) is one mechanism to reduce missing data, reduce patient burden and to allow for more frequent collection.
- Whilst some clinical aspects of the Gaucher disease do not apply to oncology, pain, fatigue and activity measurements are relevant to oncology patients

RWD with technology challenges

- Data privacy and protection is key
- Electronic Health Record
- Data standardization and core dataset

Conclusions

Digital health is an exciting and rapidly evolving field

The oncology community have the optimal operational and clinical settings to use technology

Technology allows to bridge routine clinical care and clinical research, but regulatory requirements should be anticipated as early as possible.

Thank You

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