BBS Spring seminar

Transforming drug development

May 24, 2022 from 14:00-17:45

Novartis Campus, Auditorium 510_U1

Agenda

14:00 – 14:10	**Welcome,** Uli Burger, BBS President
14:10 – 15:00	**Why is transformation of drug development needed?**
	Chair: Achim Güttner, Novartis Pharma development perspective: Guy Braunstein, Pierre Verweij, Idorsia Investor perspective: Pavithra Rallapalli, Colin Terry, Deloitte
15:00 – 15:30	***Coffee break***
15:30 – 16:30	**Areas of innovation in drug development: case studies and future vision**
	Chair: Fred Sorenson, Xcenda Real-world data: Dominik Heinzmann, Novo Nordisk External controls : Lisa Hampson, Sebastian Weber, Novartis Digital biomarkers: Laurent Essioux, Roche
16:30 – 17:15	**Panel discussion**
	Chair: Marcel Wolbers, Roche Panel: All speakers, Lorenzo Hess, Swissmedic, and Frank Bretz, Novartis
17:20 – 17:45	**BBS general assembly**

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Transforming drug development: is it needed?

Pierre Verweij and Guy Braunstein, Idorsia Pharmaceuticals

BBS Spring Seminar – 24 May 2022

Disclaimer

- This presentation reflects the views of the presenters today and may not represent the views or policies of Idorsia.

Transforming drug development

- Most calls for transformation focused on costs…
  - A proposal for radical changes in the drug-approval process (NEJM, 2006)
  - Time for reform in the drug development process (Lancet, 2008)
  - The $2.6 billion Pill – Methodologic and policy considerations (NEJM, 2015)
  - A much-needed corrective on drug development costs (JAMA, 2017)
  - Regulating drug prices while increasing innovation (NEJM, 2021)

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Transforming drug development

- ...some focused on doing things 'smarter'

  - Pharmacogenetics and future drug development and delivery (Lancet, 2000)
  - Accelerating drug discovery (Lancet, 2014)
  - Seamless Oncology-Drug Development (NEJM, 2016)
  - Will precision medicine move us beyond race? (Lancet, 2016)
  - Pharma blockchains AI for drug development (Lancet, 2019)

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Transforming drug development

- Transforming drug development is, obviously, not something that can be driven by statisticians alone
  - Hence, this joint presentation

- Nor is it something that can be driven by one company alone or even by pharma alone
  - We need regulators, payers, the medical community and patients on board

- But we have a few ideas

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Are drug development costs *too* high?

- Costs
  - Cost to be interpreted in the context of potential revenue
  - Driven by monitoring (≈ 50%), investigator's cost (≈ 25%), central lab and other central activities (≈ 10% to 15%), biometry (≈1% to 3%)
  - Apparent cost is high due to high development failure, inappropriate decisions (based on small, underpowered, poorly informative studies), and inclusion of opportunity cost (cost of capital) in calculation
  - Real cost may be more acceptable; concern resides in cost of "doing" vs. cost of "thinking"

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Are drug development costs *too* high?

- *Time* is the main cost driver
  - Time to obtain regulatory and EC approval
  - Administrative time and slow site initiation (e.g., contracting)
  - Studies are larger and longer because of the need to document potential safety risks and because of smaller incremental efficacy
  - Slower recruitment rates: investigator's inertia, lack of scientific motivation?
  - "Lost" time: interactions with regulatory agencies and especially payers

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Are drug development costs *too* high?

- *Complexity* is another cost driver
  - Strict selection criteria in our trials
    - To give the drug the best chance (not per se focused on patients)
    - As a result, only a fraction of potential patients are included in a clinical trial (e.g., in oncology 5%). Minorities are underrepresented.
  - Reluctant to drop measurements that have no proved added value in previous trials: continue to measure 'just in case'
  - Hesitance to be simple and pragmatic (i.e., collect only limited data)
  - Tendency to collect more extensive or more complex data (AI-driven analysis)

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Competition and value to society

- Tougher competition
  - We all compete for the same patients
  - Only a small proportion of patients enter studies
  - Incremental value of many products questionable: “me too” or “small +”
    - How many times should we repeat success (even though replication is needed)?
    - How many times should we repeat failure (replication needed here as well)?

- As an industry, are we relevant and productive:
  - Are we delivering value to patients and public health?
  - Are we giving back to the society what we owe?
  - Are we efficient?

Possible directions

- Where can study design, study conduct, and analysis help to address the aforementioned issues?

- Save time by combining different study phases in one study
  - Seamless Phase 2-3 trials and other adaptive designs: is it really efficient and is it really used? No time for learning.
  - Combine proof-of-concept (Phase 2a) and dose-finding (Phase 2b)

- Save administrative time by master protocols

- Real world data, external controls, biomarkers – also covered in the next presentations

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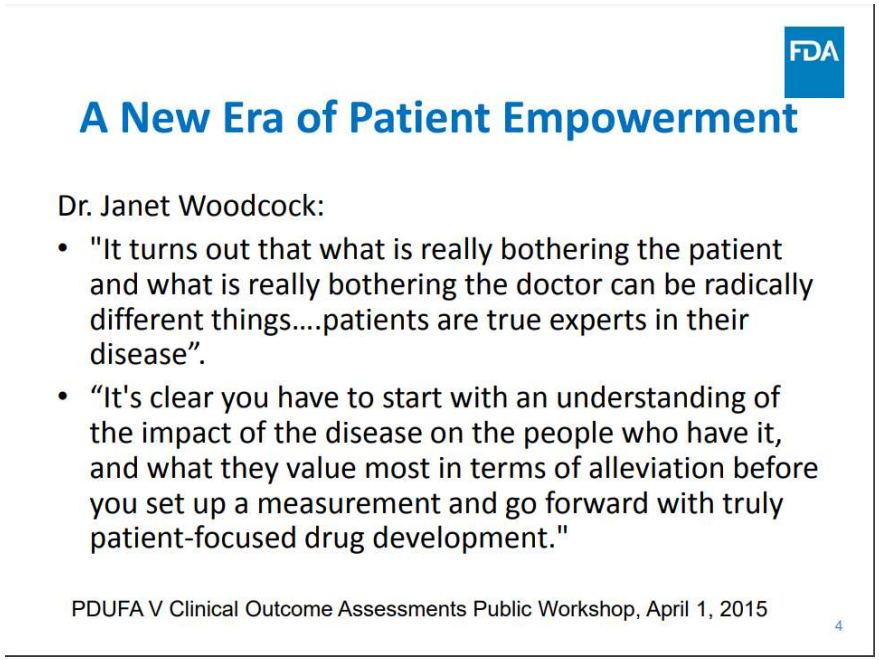
Directions (i) : efficiency - revisit the “doing” ?

- Do we need centralization of … randomization, drug supplies, laboratory, ECG, lung function, adjudication of events… what is the added value?
- Low recruitment rate: can it be improved?
  - Role of patients and patients’ advocacy groups?
  - Investigator’s motivation
- The technology:
  - Monitoring visits vs. central monitoring in the era of eCRF?
  - Can we question the added value of some of the technologies: e.g. eTMF?
  - Do we use technologies appropriately?

Directions (ii) : being more relevant to patients

- Objective: measure and determine how patients feel, function, and survive



- Understanding the medical condition (including from patient's view)
- Conceptualize the benefit (including from patient's view)
- Create outcome measures (including from patient's view)
  - Patient-reported outcome
  - Patient's values and preference

Directions (iii) : keeping science strong

A few examples (only)

- Efficacy objective has not changed: measure and determine how patients feel, function, and survive

- Issue 1: A group of patients, rather than individuals, is at the center of the analysis
  - Marginal gains
  - Group delta smaller than individual delta

- Issue 2: Biomarker rather than clinical endpoint
  - On the pathophysiological pathway
  - Or a simple curiosity

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Directions (iii) : keeping scientific and strong

A few examples (only)

- Issue 3: Real-world data rather than randomized clinical trials
  - RWD do not deliver evidence
  - (Limited) place of RWD to be strictly defined
  - Will not replace RCT: more, not less well-designed, well-conducted, relevant and efficient randomized trials are needed

- Issue 4: new technologies (AI, machine learning)
  - Wearable devices generate big data
  - To clinicians even more ‘black box’ than statistical modelling

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Conclusion

- Is transformation of drug development needed or just evolution?
  - There may be more serious issues than cost and time:
    - Are we producing efficiently new medicines, bringing substantial efficacy and safety increment?
    - Are we fulfilling our mission of discovering, developing and commercializing new therapies that can help patients feel better, function better and survive longer?

- Possible directions to stay relevant and sustainable:
  - Keep the science at the heart of the process, in particular in decision making
  - Place patients at the center of our work
  - Be more efficient in the process

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Deloitte.

BBS Seminar – May 2022

Transforming Drug Development

Colin Terry | Dr Pavi Rallapalli

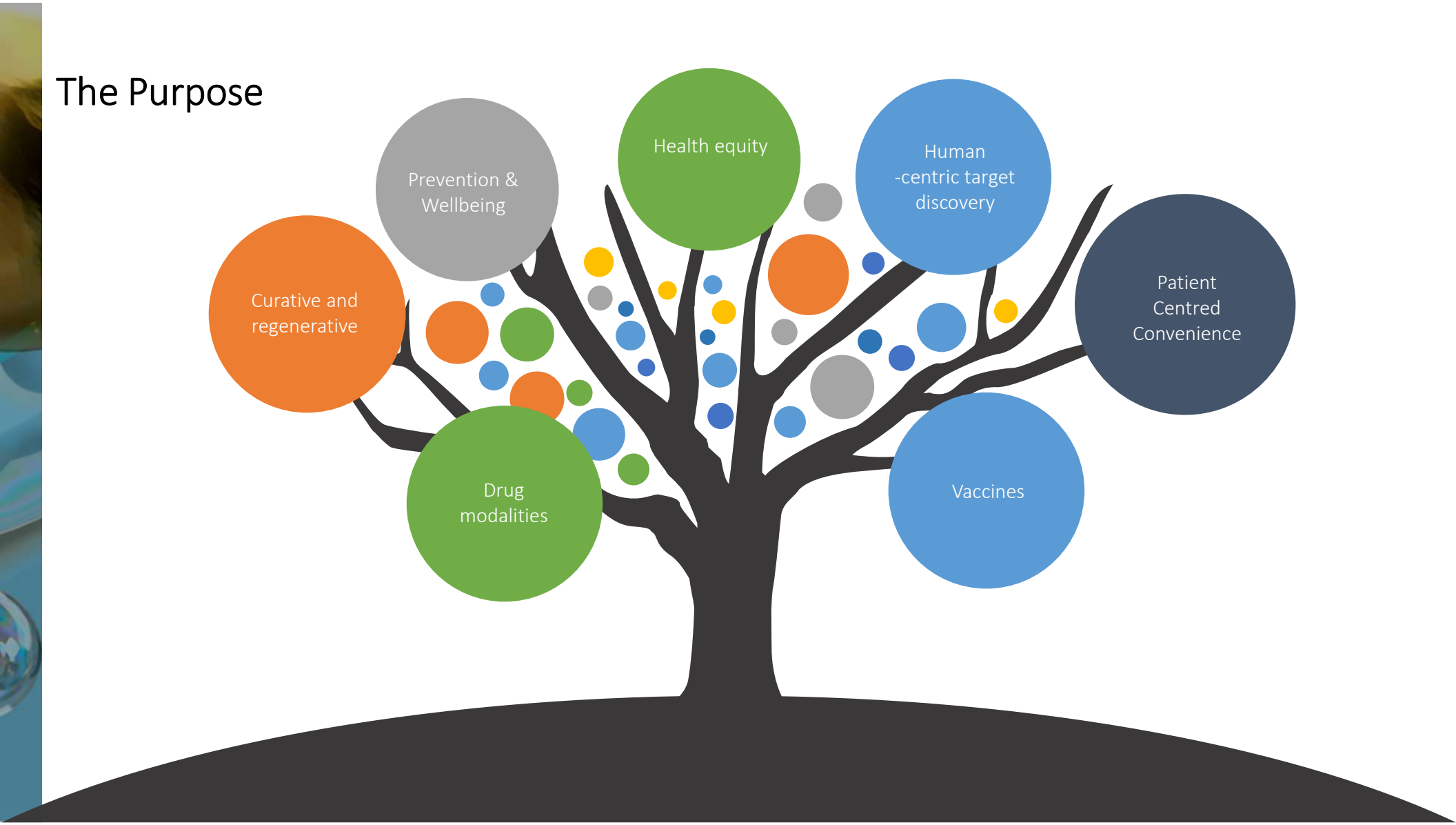
Colin Terry

- *R&D Leader*
- *Life Sciences Consulting Lead*
- *Deloitte*

Dr Pavi Rallapalli

- *Precision Medicine and RWE Leader*
- *Health Data and AI Lead*
- *Deloitte*

The Purpose


Prevention & Wellbeing
Health equity
Human -centric target discovery
Curative and regenerative
Patient Centred Convenience
Drug modalities
Vaccines

Transforming Drug Development is essential to keep up with the changes in the business model of Pharma

The fundamental business model has changed over the last two decades and the next decade will challenge market leaders' ability to adapt

2000-2010

Rise of primary care beyond public health agenda

- Therapy area growth **focus on primary care** diagnosis and delivery
  - CV, GI, Respiratory, Psychiatry,
  - Communicable diseases diminishing in West
- **Expanding scale of R&D functions** and geographies
- **CROs establish and grow** with focus on primary care footprint
- **Platforms as scale enabler** (e.g., high throughput screening)

2010-2020

Shift from the many to the few

- TA **growth moves to specialists and advanced tools** e.g., imaging and sequencing
  - Oncology, Rare Diseases
- NCE transition to **NBE**
- **Regulators in transition** from narrative investigators to data analysts
- **"Peak" R&D in the West**
  - Spend by major players breaks trend with sales growth
  - "China for China"
  - R&D headcount reductions post M&A and therapy failures

2020-2030

The rise of cure and personalised health

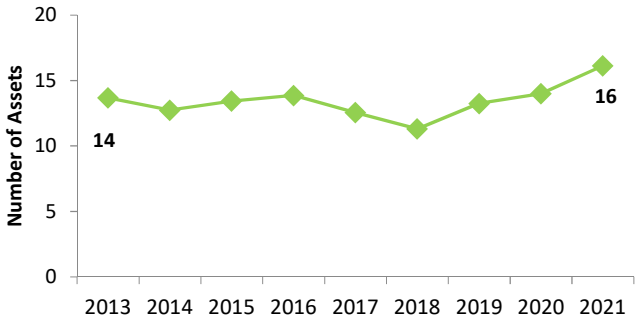
- **What are the drivers of the winning business model?**
  - Capital allocation choices for divergent businesses
- **How to dramatically reduce the cost per asset?**
  - What is the cost base design?
  - Enterprise thinking of IRR?
- **What is beyond chronic care in the current TAs?**
  - Chronic vs Curative?
  - Creating new value TAs?

Why is transformation of Drug Development needed?

The discovery of new drugs is an undeniably important undertaking and represents a massive global market

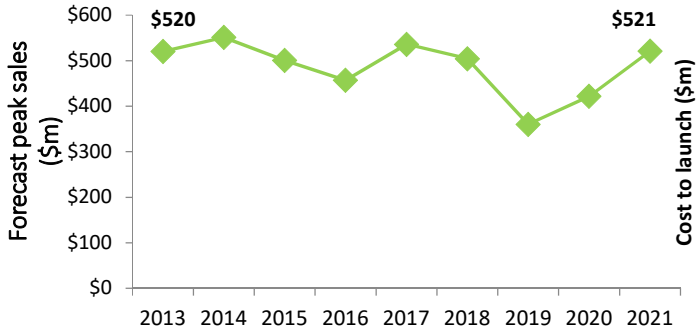
Return on Investment | Disruptive Digital Intervention | Health equity | Speed | Next Generation Therapy | Holistic Precision Medicine | Sustainability

Insights from Deloitte R&D benchmarking report



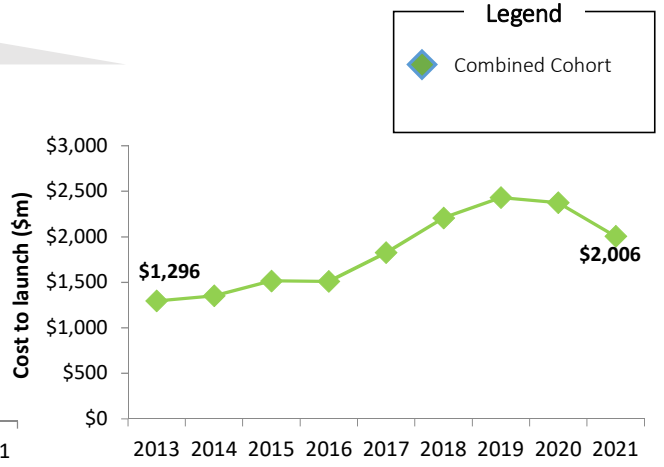
Number of late-stage pipeline assets

$= \Sigma(unique\ late\text{-}stage\ molecules)$



Forecast average peak sales per asset

$$= \frac{(Total\ risk\ adjusted\ peak\ sales\ for\ all\ assets)}{N^o\ assets}$$

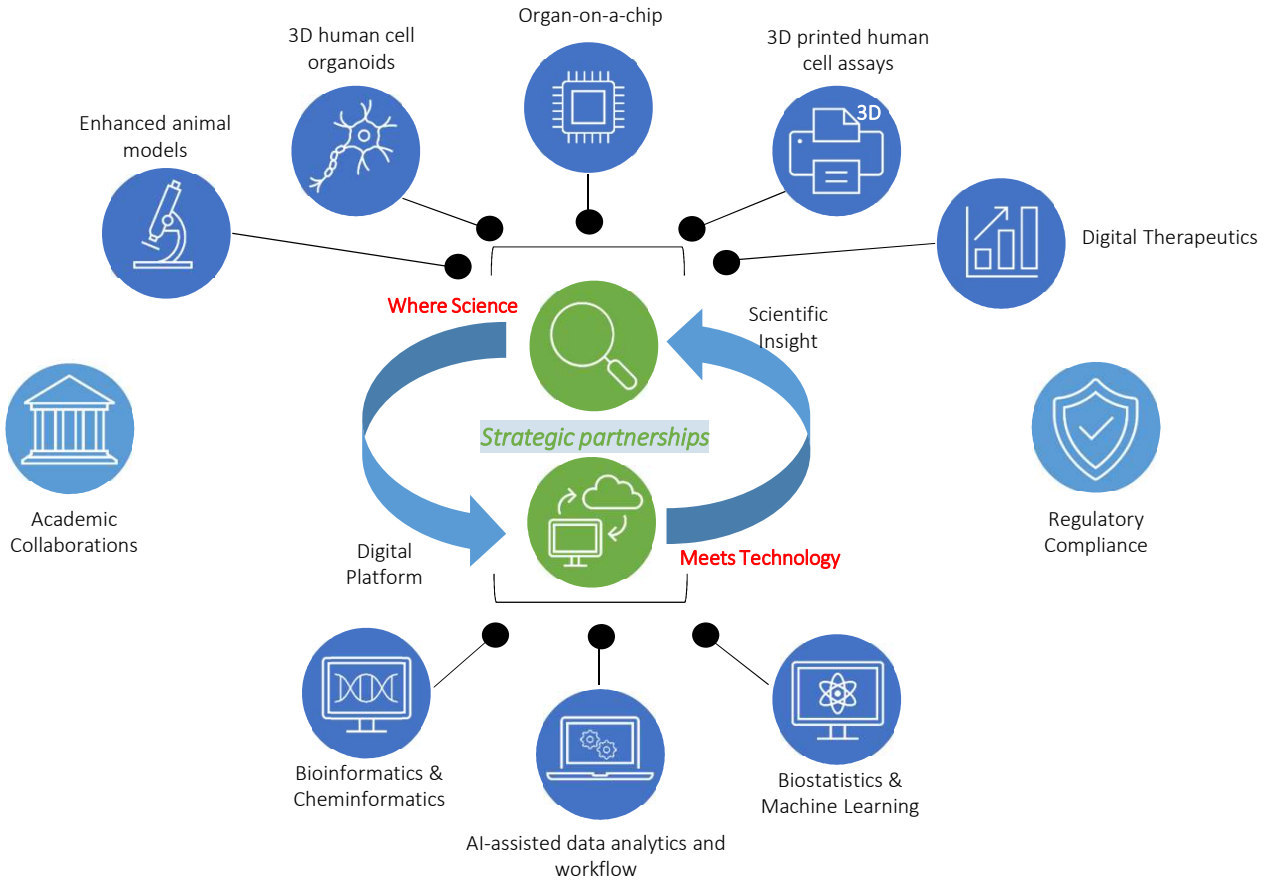


R&D cost to bring an asset to market

$$= \frac{(Total\ phase\ adjusted\ R\&D\ cost + deal\ costs)}{N^o\ assets\ * PTRS}$$

At the heart of this transformation is enabling *"Science meeting Technology"*

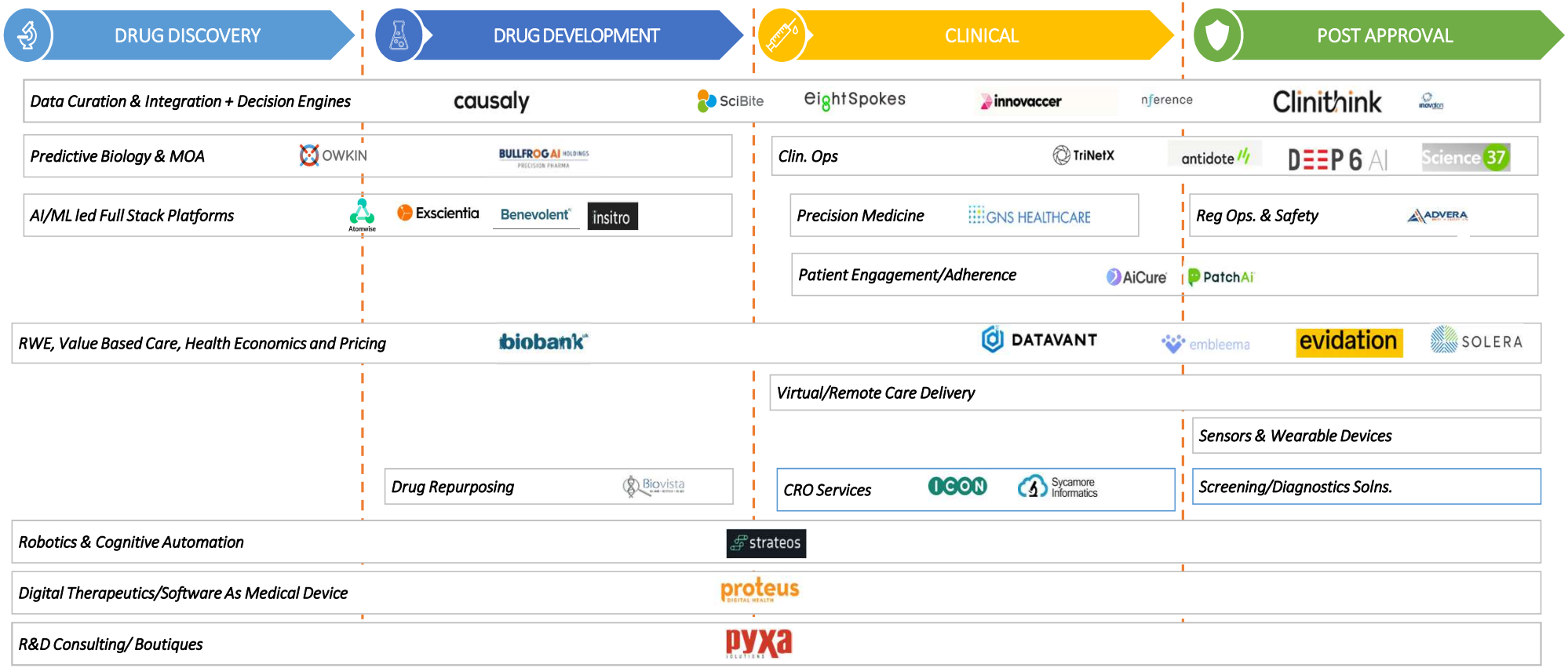
Paving the way for the future of Drug & biomarker discovery, Platform-based technologies and integration of Pharma and Non-Pharma organisations



SOURCE: DELOITTE RESEARCH

The R&D Innovation Landscape: Non Pharma Startups

Accessing external innovation continues to be a high priority with a number of emerging start-ups driving solutions



SOURCE: CAPITAL IQ, DELOITTE RESEARCH

The R&D Innovation Landscape: Platform-based technologies

Platform technologies are considered a valuable tool to improve efficiency and quality in drug product development. Such platforms enable a continuous improvement by adding data for every new molecule developed by this approach, which increases the robustness of platform.

Type of Platforms & Technologies	Key Players
Antibody Drug Conjugates	REGENERON, Seagen, Roche, Pfizer
Antibody Engineering/Multi-specific Antibodies	J&J, Bristol Myers Squibb, Lilly, SANOFI
Peptide-Drug Conjugates	ascendis pharma, PeptiDream, ACCELERON, ALMAC
Gene Editing / CRISPR	Beam Therapeutics, CRISPR Therapeutics, BIOMARIN, VERTEX, Roche
mRNA	moderna, BIONTECH, CUREVAC
RNAi	Alnylam, arrowhead pharmaceuticals, Dicerna, horizon
Stem Cell Therapy (iPSC, MSC etc.)	Fate Therapeutics, LEGEND BIOTECH, PHARMICELL
Autologous Cell Therapy (Car-T, Car-NK etc.)	LEGEND BIOTECH, NOVARTIS, GILEAD

- Access to blockbuster drug technology and complementing TA focus have been traditional drivers for platform transactions.
- Most platform deals continue to be co-development collaborations and licensing arrangements rather than outright acquisitions, however there is a shift in attitude towards acquiring platform-based technology in the recent years.

Select Platform-based M&A Activity

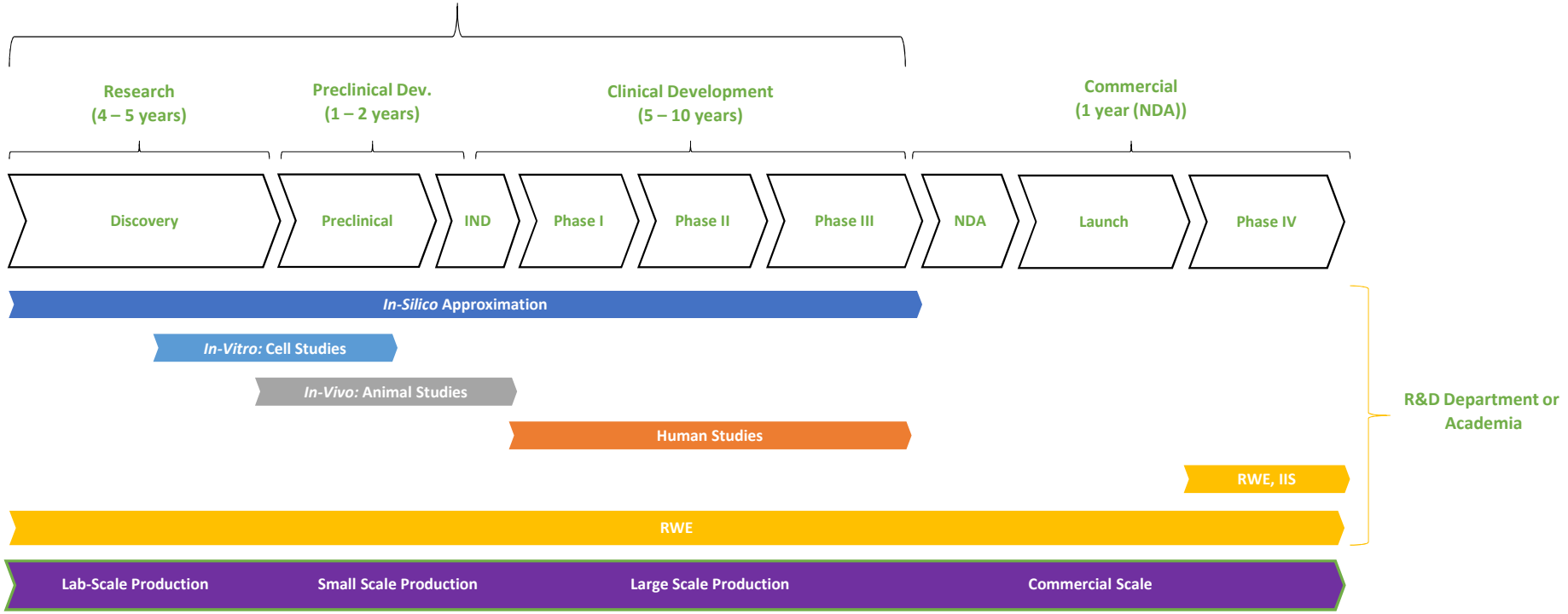
Announcement Date	Target	Acquirer	Transaction Size ($B)	LTM Revenue Multiple	LTM EBITDA Multiple	Premium % (1-Week)	Platform / Technology
December 2021	GYROSCOPE	NOVARTIS	$1.5	n.m.	n.m.	n.m.	AAV Gene Therapy
November 2021	Dicerna	novo nordisk	$3.2	14.2x	n.m.	73%	GalXC RNAi
August 2021	TranslateBIO	SANOFI	$3.1	11.4x	41.8x	13%	mRNA Tech
August 2021	vividion THERAPEUTICS	BAYER	$2.3	45.6x	n.m.	n.a.	Chemoproteomic Platform
April 2021	PANDION THERAPEUTICS	MERCK	$1.8	181.5x	n.m.	177%	TALON Technology
October 2020	ASKLEPIOS	BAYER	$4.0	n.a.	n.a.	n.a.	AskBio AAV Technology Platform

Thank you!

Drug Development is an arduous, lengthy and costly process:

Fewer than 2.5% of discovered compounds pass screening to clinical development.

Despite the differences among companies, they generally share similar organisational processes. In general, out of 10'000 compounds "discovered," fewer than 250 pass screening to clinical development. R&D (Research, Preclinical Development, and Clinical Development) is a key part of the process and is the foundation of the Life Sciences industry.



Innovation is picking up the Pace

Exponential change will accelerate the pace of disruption

Factors influencing changes

TECHNOLOGICAL DEVELOPMENT

Moore's law: the power of chips, bandwidth and computers doubles approximately every 18 months

MOBILE PHONES:
The number of mobile phones worldwide doubled in the last
48 months

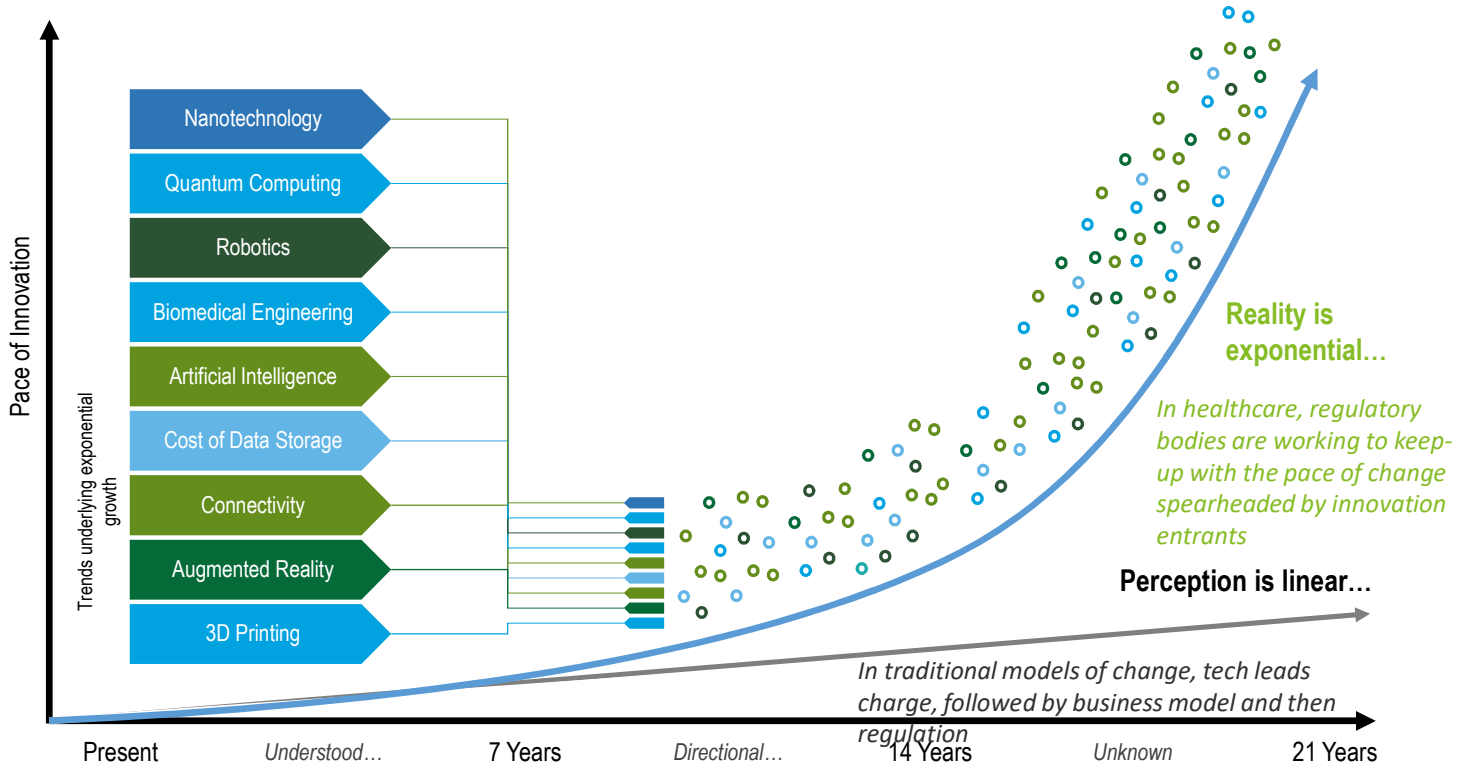
DNA SEQUENCING:
From $1 billion and 13 years to
<$100 and <1 hour

DATA STORAGE:
From $569 per GB to
<$0.01

THE HUMAN FACTOR

Technology development feeds and enables various trends in society:

Resulting Impact



Areas of innovation in drug development | **Real-World Data & Evidence**

Dominik Heinzmann, VP & Global Head Data Orchestration, Novo Nordisk

BBS Spring Seminar, 24 May 2022

Agenda

What are RWD and RWE?

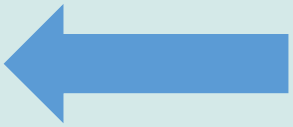
Evolving eco-system & Stakeholders

Transformation enablers

Summary

Agenda

What are RWD and RWE?



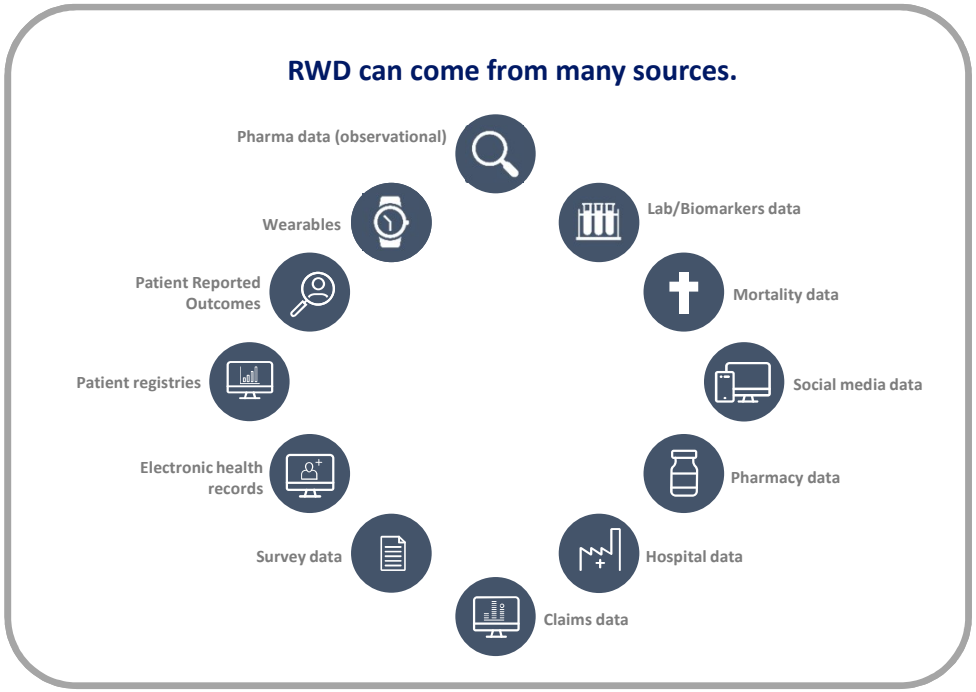
Evolving eco-system & Stakeholders

Transformation enablers

Summary

Real-World Data| RWD

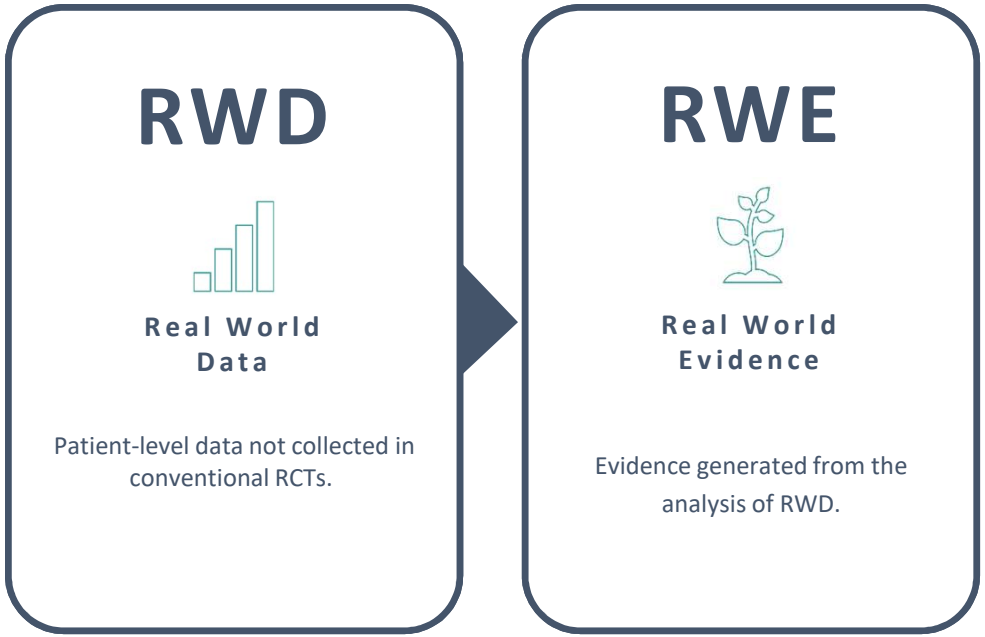
"data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources"[1]



[1]U.S. Food and Drug Administration. Framework For FDA's Real-World Evidence Program. US Department of Health & Human Services; December 2018.1

Real-World Evidence| RWE

RWE is generated through analysis of RWD



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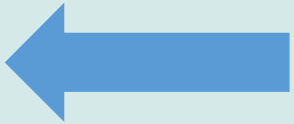
Evolving eco-system & Stakeholders



Transformation enablers

Summary

External Eco-system is shaping | Enhanced Opportunities for Innovative Integrated Solutions

Regulators worldwide work on establishing new frameworks & infrastructure for accelerating **use of RWD to supplement clinical trial data in regulatory submissions**

Patients & physicians are increasingly expecting health care to be possible via simple digital solutions

The **healthcare value chain** (e.g. physicians, providers, payors) increasingly employs clinical trial *and* real-world data **in decision making** to **increase understanding** on how medicines work in real life

The pharma industry registers **significant investments in data/digital to enable** e.g. for **more robust and faster** decision making in R&D, Regulatory, Medical and Access.

Tech companies are entering the pharma value chain with big data analytics, wearables, drug discovery tools, tele medicine etc.

Traditional use of RWE | Pillars

Understanding of the real word situation of a disease

RWE can help understand the real world situation of a disease area by identifying the target patient population, patterns of care, unmet needs and burden of disease.

Supplement evidence from RCTs

RWE can supplement evidence from RCTs by providing insights on the effects of a drug and how it is being used by patients in real life.

Monitoring of adverse events

RWE can be used to monitor post-marketing safety and adverse events of a drug.

Long-term outcomes and effectiveness

RWE can assess long-term outcomes and relative effectiveness of a medicine using existing data.

Users of RWE | Stakeholders

Industry

The industry uses RWE **throughout the lifecycle** from; identifying unmet needs, disease characteristics and optimisation of clinical trial designs to advancement of treatment approaches, market access and monitoring of safety.

Regulators

Regulators give **marketing authorisation** and can use RWE to monitor long-term safety and effectiveness of a drug, e.g. to fulfil post-marketing requirements or to make label expansions. Regulators are beginning to acknowledge the value of RWE to support regulatory decision making, and in the future RWE may become an integrated part of the drug approval process.

Payers

Payers **manage cost of care and give access** to treatment via reimbursement decisions. RWE can support payers by providing an understanding of the relative and cost effectiveness of a new drug compared to standard of care in patients eligible for the new medicine in their population. In addition, RWE can inform payers about the budget impact, comparative effectiveness and safety in clinical practice.

HCPs

HCPs can use RWE in as a support tool in **treatment decision making.** RWE can provide a better understanding of the real world effect of a drug in a specified patient population. This can give physicians and HCPs more confidence in prescribing.

Patients

RWE can help patients by demonstrating how a treatment works as well as **the real benefit of it in similar patients.** This may improve the overall treatment experience and may increase the chance of patients initiating and complying with therapy if their overall experience of a drug is improved.

Sources
1. RWE-Navigator, How can RWE be used in medicine development?
2. RWE-Navigator: Why is RWE important in medicine development?
3. Oehrlein et al. 2019 Patient-Community Perspectives on Real-World Evidence: Enhancing Engagement, Understanding, and Trust

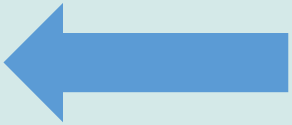
HCP: Health care professional, RCT: Randomised controlled trial, RWE: Real world evidence

Agenda

What are RWD and RWE?

Evolving eco-system & Stakeholders

Transformation enablers



Summary

Transformation enablers| RWD at scale with common data model

Vision

Establish and maintain a secure EU data platform that supports better decision making throughout the product lifecycle with reliable evidence from real world
healthcare

Vision

Aspire to be the trusted observational research ecosystem to enable better health decisions, outcomes and care

Vision

Achieve a sustainable national resource to monitor the safety of marketed medical products and expand real-world data (RWD) sources use to evaluate medical product performance.

Transformation enablers| Advanced analytics & RWD

Received: 7 July 2021 | Revised: 21 September 2021 | Accepted: 12 October 2021
DOI: 10.1002/cnr2.1578

ORIGINAL ARTICLE

Cancer Reports | WILEY

Real-world data prognostic model of overall survival in patients with advanced NSCLC receiving anti-PD-1/PD-L1 immune checkpoint inhibitors as second-line monotherapy

Cristina Julian[1] | Robson J. M. Machado[2] | Sandhya Girish[1] | Pascal Chanu[3] | Dominik Heinzmann[4] | Chris Harbron[2] | Anda Gershon[1] | Shannon M. Pfeiffer[1] | Wei Zou[1] | Valerie Quarmby[1] | Qing Zhang[1] | Yachi Chen[1]

Evaluating eligibility criteria of oncology trials using real-world data and AI

Ruishan Liu, Shemra Rizzo, Samuel Whipple, Navdeep Pal, Arturo Lopez Pineda, Michael Lu, Brandon Arnieri, Ying Lu, William Capra, Ryan Copping ✉ & James Zou ✉

Nature **592**, 629–633 (2021) | Cite this article

KICS The Korean Institute of Communications and Information Sciences

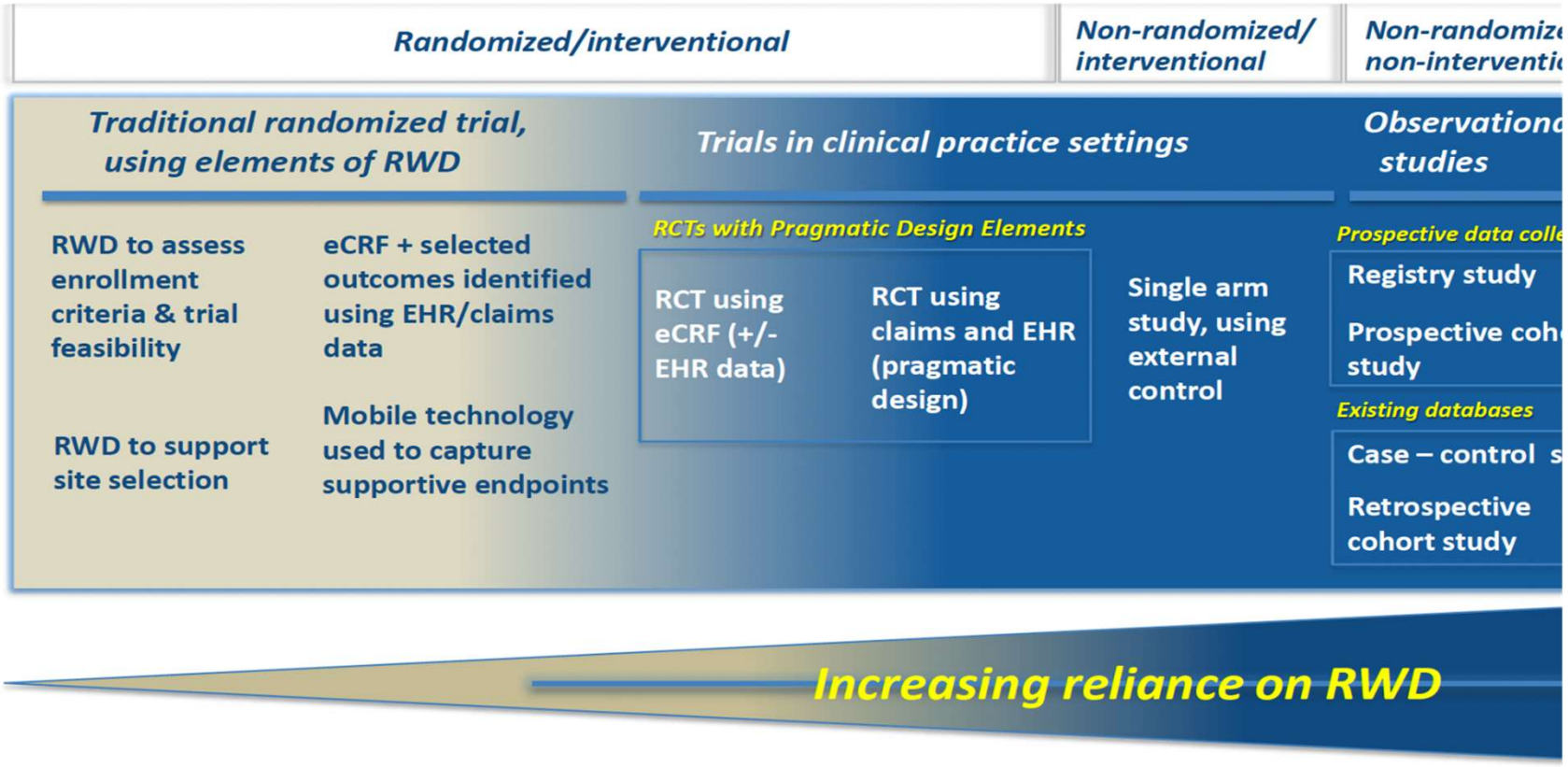
Available online at www.sciencedirect.com
ScienceDirect
ICT Express 7 (2021) 432–439
www.elsevier.com/locate/icte

A comparison of machine learning algorithms for diabetes prediction

Jobeda Jamal Khanam, Simon Y. Foo*
Department of Electrical and Computer Engineering, FAMU-FSU College of Engineering, Tallahassee, FL 32310, USA

Received 20 August 2020; received in revised form 2 January 2021; accepted 11 February 2021
Available online 20 February 2021

Transformation enablers | Innovative trial designs



RCT- randomized clinical trial
eCRF - electronic case report form

Jacqueline Corrigan-Curay, JD, MD, The FDA Real-World Evidence (RWE) Framework and Considerations for Use in Regulatory Decision-Making, May 2021

Transformation enablers | RWD endpoints

- **Examples:**
  - General: Overall survival
  - Oncology & haematology: Real-world progression (radiology-anchored, clinician-anchored) …
  - Cardiovascular disease: CV event (stroke, MI…)
  - Diabetes: New or worsening nephropathy

- **Challenges**
  - Patient care in the real-world setting is **not standardized**
  - Data source used for developing RWD endpoints such as EHR have **limitations**

- **Opportunities**
  - **Collaborations:** Sentinel, IMI EHDEN, EU Darwin - common data models / computational phenotyping
  - **Guidance documents:** WHITE PAPER: Duke-Margolis[1]
  - **Fit-for-purpose:** Develop RWD endpoints with research question in mind, using it in conjunction with tools like the estimand and target trial framework
    - RWD endpoint use in external control setting vs Registry-embedded trials

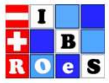
[1]Duke-Margolis Center for Health Policy, 2020, " A Roadmap for Developing Study Endpoints in Real-World Settings"

Transformation enablers | Combining (causal) inference frameworks

Using The Estimand And The Target Trial Frameworks When Building An External Control From Real-World Data: A Case Study In Oncology

Letizia POLITO[1*], Qixing LIANG[2*], Navdeep PAL[3], Philani MPOFU[2], Ahmed SAWAS[2], Olivier HUMBLET[2], Kaspar RUFIBACH[1], Dominik HEINZMANN[1]

[1]F. Hoffmann-La Roche Ltd, Switzerland; [2]Flatiron Health, New York, NY, USA; [3]Genentech, Inc., South San Francisco, CA, USA; *co-first authors



Conference of the Austro-Swiss Region (ROeS) of the International Biometric Society
7 - 10 September 2021 | Salzburg, Austria

CONCLUSION

- **This requires a new mindset:**
  - Re-define importance of variables not previously collected in the real world (e.g. intercurrent events)
  - Become familiar with the strategies to address intercurrent events
  - As per ICH E9 addendum, think carefully on what constitutes sensitivity analyses vs supplementary analyses for the key estimand also in observational research

Agenda

What are RWD and RWE?

Evolving eco-system & Stakeholders

Transformation enablers

Summary

Summary | Some personal thoughts

- **TODAY:** Transformation in drug development ongoing: RWD plays a critical role

- **TOMORROW:**
  - Data (more) at scale, multi-modal (imaging, omics,…), using common data models
  - More population-based platforms at a geographic (not patient) level to look at entire eco-systems (eg demographics, epidemiologic, disease, mobility, environmental…)

- **FUTURE STATE:**
  - Quality of data significantly enhanced
  - Large uptake on randomized pragmatic trials (e.g. registry embedded trials)
  - Federated learning

[1]Duke-Margolis Center for Health Policy, 2020, " A Roadmap for Developing Study Endpoints in Real-World Settings"

THANK YOU!

Questions?

Analytics

Areas of innovation in drug development: use of external controls

Lisa Hampson, Marc Vandemeulebroecke, Heinz Schmidli, Sebastian Weber

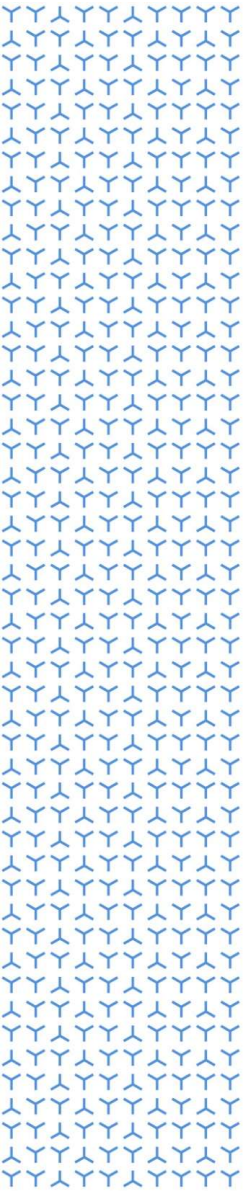
Basel Biometric Society Spring Seminar

May 24th, 2022

NOVARTIS | Reimagining Medicine

Agenda

- Introduction
- Case study – Ankylosing spondylitis
- Case study – Pediatric multiple sclerosis
- Case study – Moderate psoriasis in pediatrics
- Conclusions



Introduction

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Applications of external controls

Trial-Internal Treatment Group | Trial-Internal Control | Trial-External Control | Trial-External Simulated Control

Increasing HA Acceptance

Arm Label	Study Design	Control Data Sources (placebo / SoC)
Internal control arm		Prospectively designed RCT
Hybrid control arm		External control data (ECD) Individual patient and/or aggregate data from: ❑ Historical / concurrent RCT(s) ❑ Real-world data sources: most relevant if active control e.g. SoC; challenging to find RWD on placebo
External control arm (ECA)*		
Synthetic external control arm (SECA)		Synthetic** (simulated) data based on RWD, historical trials or other sources

* Sometimes referred to as a 'Virtual' control arm. We prefer ECA to emphasize that in these cases, the control arm is based solely on trial-*external* information.

** Sometimes referred to as 'in silico' data or digital twins

RCT = randomized controlled trial; RWD = real world data; SoC = standard of care

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Context


REVIEW

Beyond Randomized Clinical Trials: Use of External Controls

Heinz Schmidli[1], Dieter A. Häring[1], Marius Thomas[1], Adrian Cassidy[1], Sebastian Weber[1] and Frank Bretz[1,*]

- Proof of Concept (PoC) studies
  - Routine use of external controls, often to create a hybrid control arm
- Cases where traditional RCTs are less practical or relevant
  - Use external controls to create a hybrid or external control arm
  - Pediatric development programs (e.g. see draft ICH E11A guideline)
  - Rare indications
  - Situations of high unmet medical need
  - Epidemics, where the objective is to "learn as much as possible, as quickly as possible, without compromising patient care"

Schmidli et al. (2021)

Other applications of external controls

Optimize trial design and conduct:

- Derive more accurate estimates of nuisance parameters and inform sample size calculations
- Specify the non-inferiority margin or null hypothesis of a single-arm trial*

Understand disease setting by using external controls to:

- Improve our understanding of competitor performance
- Inform the specification of Target Product Profile (TPP) thresholds

* Simple way to use external controls which avoids a direct comparison and estimation of the magnitude of the treatment effect.

Considerations for leveraging external controls

Benefits	Risks
✓ Avoid replication of existing evidence ✓ Reduce # of placebo patients in new trial ✓ Decrease costs ✓ Accelerate access to new medicines ✓ Facilitate recruitment ✓ May be more ethical in some situations	— Conflict between external and internal controls threatens internal validity — Biased estimates of causal effects — Excessive type I error rate — External controls may not provide information on all needed endpoints

Take steps to eliminate or mitigate biases. E.g.

- Systematic & reproducible selection of external controls
- Robust priors, adaptive designs
- Leverage methods of causal inference
- Aligning design and analysis with objective

See also Burger et al. (2021)

Case study 1

Proof of Concept (PoC) study in ankylosing spondylitis

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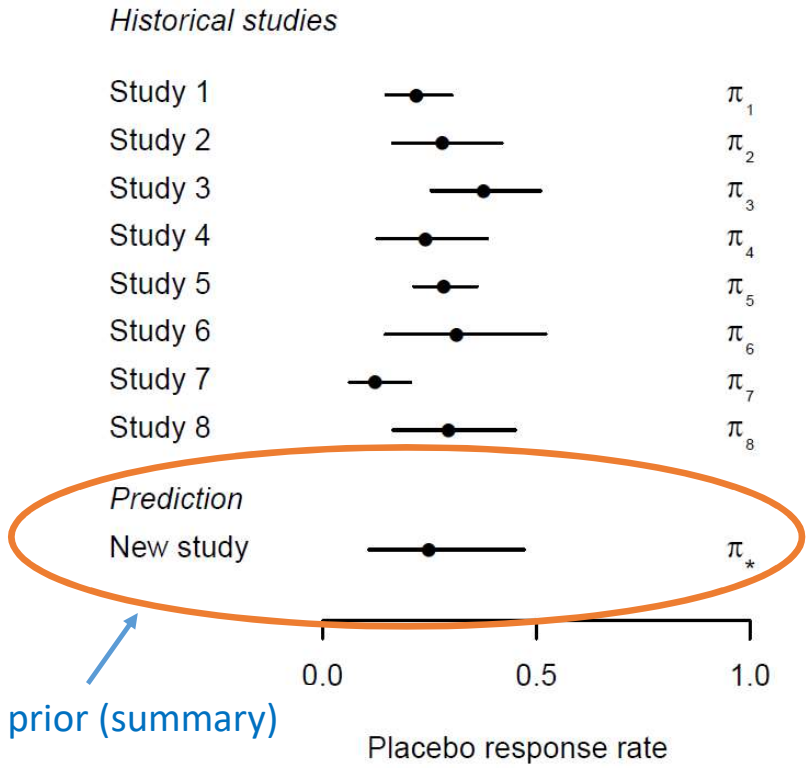
Leveraging external controls in a PoC study

- Disease: Ankylosing spondylitis
- Treatments: Cosentyx (test) vs placebo (control)
- Endpoint: ASA20 response at week 6
- Data: Placebo (aggregate data) from ...
  - ... 8 RCTs; total 533 patients
- Method: Meta-analytic-predictive (MAP) prior for placebo response rate in new study
  - Accounts for between-study heterogeneity
  - Effective sample size = 43 patients
- Place a weakly informortive prior on Cosentyx response rate.



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Conclusions

- Historical placebo information allowed us to reduce the number of patients randomized to placebo:
  - Stand-alone RCT: Cosentyx (n=24) and placebo (n=24)
  - RCT+external controls: Cosentyx (n=24) and placebo (n = 6) + external controls
- Moving away from 1:1 randomization may facilitate recruitment
- Leveraging external controls could become standard practice for PoC studies:
  - Sponsor has more freedom with early phase trial design (sponsor's risk)
  - Greater regulatory acceptance of leveraging external controls in this context
  - Standard approach for PoC studies in Novartis (where scientifically feasible)

Case study 2

Development program in pediatric multiple sclerosis (MS)

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Clinical trials in rare diseases

- Challenge to recruit patients with rare disease for RCT comparing a test treatment with a control treatment

Hampson et al. (2014); Friede et al. (2018); Ramanan et al. (2019)

- Pediatric Multiple Sclerosis (MS)
  - Characterized by recurrent relapses
  - Rare disease (US: about 5'000 children vs 800'000 adults with MS)
  - High unmet medical need with 15+ approved therapies in adults, but only 1 in children (fingolimod) based on only completed RCT trial (PARADIGMS, Chitnis et al. 2018)
  - Slow recruitment, with on average <1 patient recruited per year and per center
  - Clinical trials are considerable burden to children and caregivers

Randomized trial in children with MS

- Treatments: ofatumumab (test) vs fingolimod (control)
- Primary endpoint: Annualized relapse rate (ARR)
- Data: Individual patient data from ...
  - ... 3 RCTs of fingolimod in adults; total 1212 patients*
  - ... 1 RCT of fingolimod in pediatrics; total 107 patients*
  - ... 2 RCTs of ofatumumab in adults; total 946 patients*
- Method: Robust meta-analytic-predictive (MAP) approach
  - Specify informative priors for parameters of negative binomial model
  - For each adult trial, extrapolate to estimate ARR for children (age 15.3 years)
  - Use MAP approach to synthesize observed and / or extrapolated evidence in children
  - Add vague mixture component to obtain robust MAP prior

* Number of patients randomized to fingolimod (0.5mg) and ofatumumab

Conclusions

- Proposed design for pediatric MS trial has been evaluated under the Complex Innovative Designs pilot program by US Food and Drug Administration (FDA). Link
- Accepted design includes a third arm (siponimod), also borrowing information from adults
- Benefits of leveraging trial-external data in this project:
  - Reduced sample size by ≥ 30% for non-inferiority design comparing ofatumumab and siponimod vs fingolimod
  - More efficient design which is less burdensome for patients without sacrificing scientific rigor
  - Design accepted by FDA, EMA and PDCO for pediatric MS.
- Reference: Schmidli et al. (2021)

Case study 3

Pediatric development program for Cosentyx in psoriasis

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Pediatric development plan (2014)

Study 1
Severe ped. psoriasis, n=160

- High dose
- Low dose
- Placebo
- Etanercept

Study 2 (after Study 1)
Moderate ped. psoriasis, n=120

- High dose
- Low dose
- Placebo

Note: simplified design sketches

Pediatric development plan (2017)

Study 1 (already running)
Severe ped. psoriasis, n=160

Study 2 (after Study 1)
Moderate (+sev.) ped. psoriasis, n=80

Note: simplified design sketches

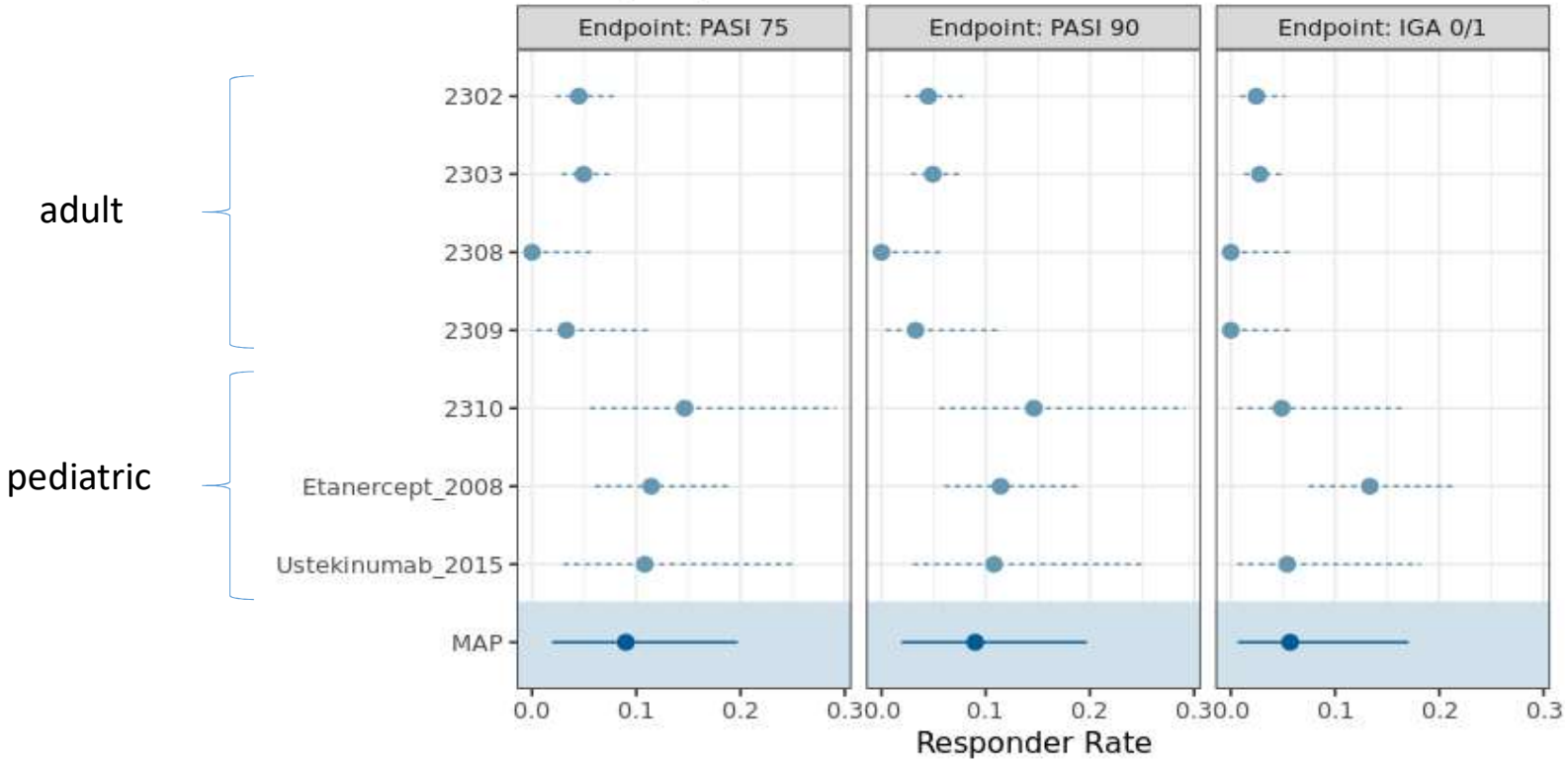
Efficacy in moderate pediatric psoriasis

- Efficacy in moderate pediatric psoriasis was established based on:
  - Extrapolation from Study 1 (severe ped. psoriasis) + adult data (severe + moderate)
    - ➢ Allowed to speed up the regulatory process in absence of Study 2 data
  - Comparison vs. historical placebo: primary analysis of Study 2
  - Exposure-response analyses (consistency across age groups and severities)
  - All pre-specified before database lock
  - Reference: You et al. (2022)

Comparison vs. historical placebo

- Data: Placebo data (summary level) from...
  - ...4 trials in adults (Novartis); total 690 patients
  - ...3 pediatric trials: Study 1 (Novartis, not available when planning) + 2 trials (literature); total 180 patients
- Method: Meta-analytic predictive (MAP) approach
  - Predicts the placebo response in a new trial
  - Available information is discounted to account for between-trial heterogeneity
  - Here, data from adults was discounted more than pediatric data
  - Implemented with RBesT R package on CRAN, Weber et al. (2021)

MAP prior derivation



Results

Log odds ratio (95% credible interval)

Endpoint	Method	Low dose	High dose
PASI 75	Extrapolation [1]	3.41 (2.29, 4.59)	3.59 (2.42, 4.79)
	Comparison vs. historical placebo [2]	4.86 (3.42, 6.78)	4.84 (3.42, 6.77)
PASI 90	Extrapolation [1]	4.82 (3.46, 6.30)	5.09 (3.73, 6.55)
	Historical placebo comparison [2]	4.37 (2.92, 6.20)	4.71 (3.20, 6.58)
IGA 0/1	Extrapolation [1]	4.08 (2.78, 5.40)	4.14 (2.87, 5.48)
	Historical placebo comparison [2]	4.29 (2.64, 6.51)	4.61 (2.92, 6.78)

[1] based on Study 1 + adult data (before Study 2)

[2] Study 2 vs. MAP prior

Conclusions

- Use of external controls embedded in a wider effort
  - Including extrapolation and exposure-response analyses
  - Dynamic process over years, facilitated by Cosentyx' strong efficacy, accumulating evidence on excellent safety, and emerging scientific innovation & regulatory openness
- EMA accepted submission dossier for moderate + severe pediatric psoriasis (incl. extrapolation results) in absence of any data for moderate psoriasis (Study 2)
  - Data from moderate psoriasis (Study 2) was included in FDA submission, and also shared with EMA during review procedure
- FDA and EMA accepted omission of placebo arm from Study 2 and approved Cosentyx for moderate + severe pediatric psoriasis
  - Data from Study 2 appears in EMA label but not FDA label (since no concurrent placebo)
  - PIP completion >2 years earlier

You et al (2022)

Final remarks

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Final remarks

- Statistics plays a leading role at various stages of using external controls, e.g.
  - Evaluating whether external controls are fit-for-purpose
  - Study design and analysis
  - Sensitivity analyses to evaluate robustness of conclusions to violations of assumptions
- Statisticians need to bring on-board cross-functional team (incl. clinical, regulatory, ...)
- Additional opportunities to leverage external controls ...
  - Dose-response studies
  - Exploiting information on baseline covariates (when available) may help to explain more between source heterogeneity and facilitate increased borrowing
- Our case studies leveraged trial-external data from RCTs
  - Synthesizing controls from RCTs and RWD may increase the pool of available data ...
  - ... but requires careful consideration of potential biases to ensure internal validity

References

- You, Weber, Bieth, Vandemeulebroecke. *Clinical Pharmacology & Therapeutics, 2022;111*(3):697
- Burger, Gerlinger, Harbron, Koch, Posch, Rochon, Schiel. *Pharmaceutical Statistics*, 2021; 20(6):1002
- Weber, Li, Seaman, Kakizume, Schmidli. *Journal of Statistical Software*, 2021;100(19 SE-Articles):1. Link
- Schmidli, Häring, Thomas, Cassidy, Weber, Bretz. *Clinical Pharmacology & Therapeutics,* 2020;107(4):806
- Hampson, Whitehead, Eleftheriou, Brogan. *Statistics in Medicine,* 2014; 33(24):4186
- Friede, Posch, Zohar, Alberti, Benda, Comets et al. *Orphanet Journal of Rare Diseases,* 2018;13 (186)
- Ramanan, Hampson, Lythgoe, Jones, Hardwich, Hind et al. *PLOS ONE, 2019;*14(6):e0215739

Thank you

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Appendix

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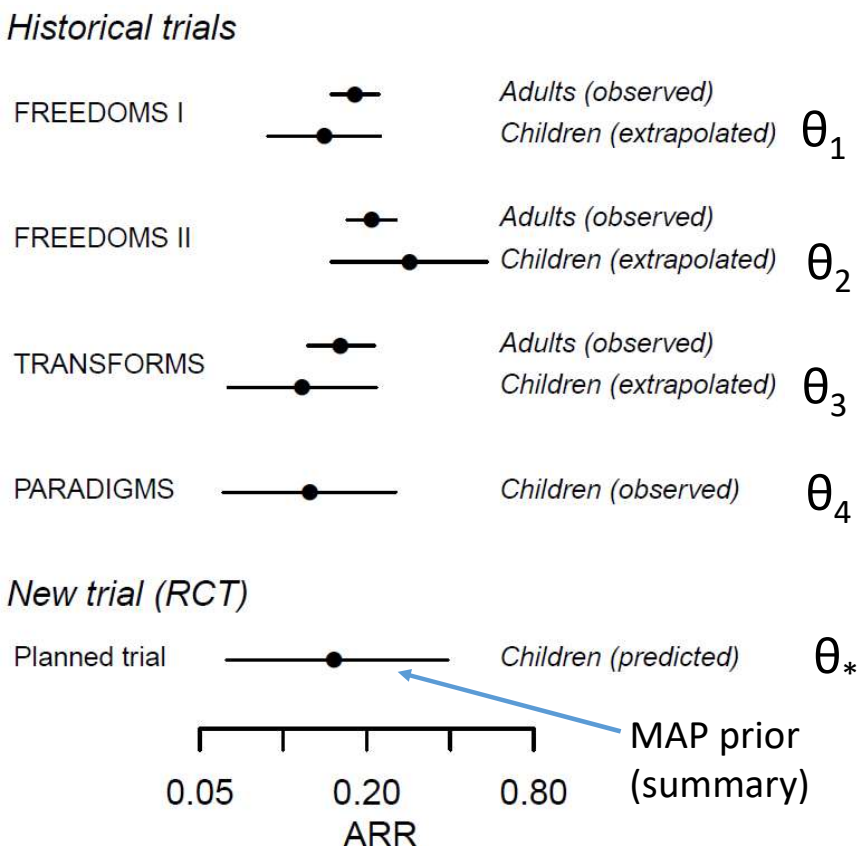
Randomized trial in children with MS

Derivation of robust MAP prior on annualized relapse rate (ARR) in planned new trial for control arm (fingolimod)

- For each adult trial, extrapolation to children (details on next slide)
- Normal meta-analytic model to link parameters: $\theta_1, \ldots, \theta_4, \theta_* \sim N(\mu, \tau^2)$

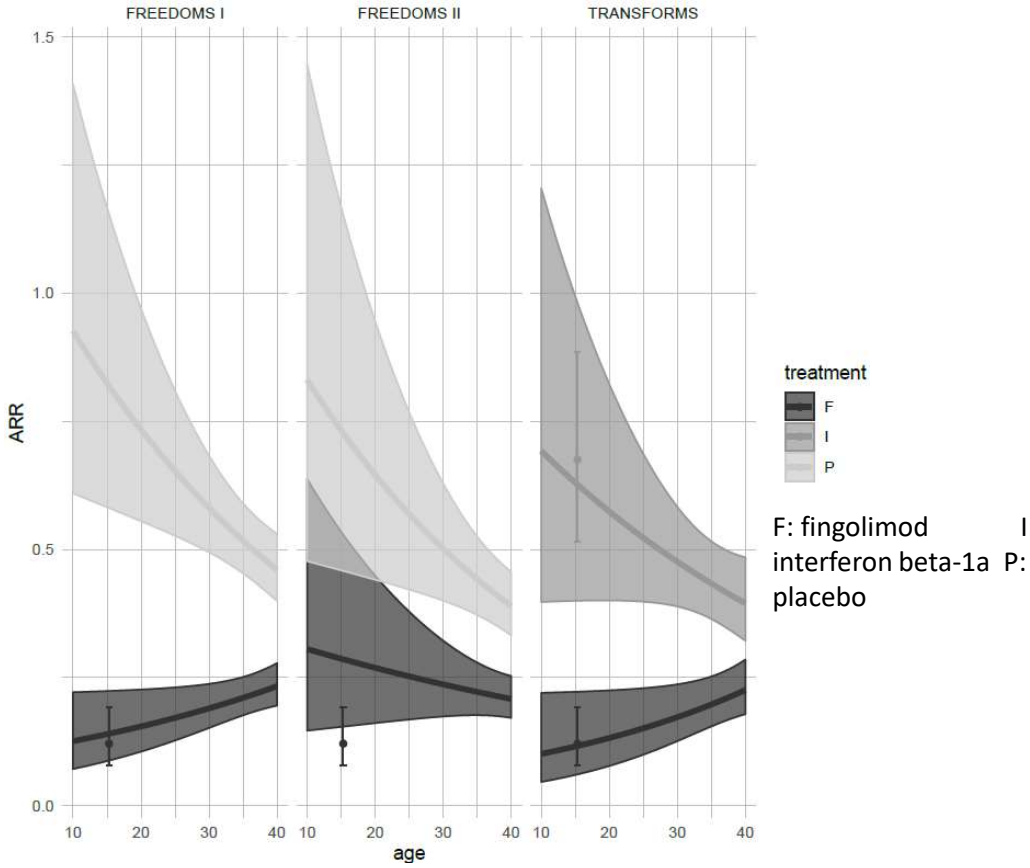
  (parameters correspond to log ARR)
- Add vague mixture component to obtain robust MAP prior



Randomized trial in children with MS

Extrapolation of ARR from adults to children:

- Children with MS are mostly teenagers (typically >10 years)
- Adult trials recruit 18+ year old
- Individual patient data were available here for all trials
- Negative binomial model on relapses, including age and relevant covariates



F: fingolimod I: interferon beta-1a P: placebo

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Statistical Model for Control Random Effects Meta-Analysis

- Binomial likelihood with trial-specific control rates per historical trial h

$$r_{i,h}|\pi_{i,h} n_{i,h} \sim \text{Binomial}\left(\pi_{i,h}, = \text{logit}^{-1}\left(\theta_{i,h}\right), n_{i,h}\right),$$

- Hierarchical model for control rates

$$\theta_{i,h}|\mu_i, \tau_{i,s(h)} \sim \text{Normal}\left(\mu_i, , \tau^2_{i,s(h)}\right),$$

- Varying between-trial heterogeneity
  - Pediatric trials: $\tau_{i,1}$
  - Adult trials: $\tau_{i,2}$

$$\tau_{i,1} \sim \text{Normal}^{+}(0,1/2^2)$$

$$\tau_{i,2} \sim \text{Normal}^{+}(0,1)$$

- Predicted pediatric control rate

$$\theta_{i,\star}|\mu_i, \tau_{i,1} \sim \text{Normal}\left(\mu_i, \tau^2_{i,1}\right),$$

A2311 Historical data borrowing

- Historical data: Previous trials of similar disease settings and characteristics
  - four Novartis reported adult placebo-controlled trials (A2302, A2303, A2308 and A2309) and pediatric study A2310, and literature with other biologics (Etanercept; Paller et al 2008, Ustekinumab; Landells et al 2015)
- Meta-analytic predictive approach (Neuenchwander et al 2010) accounts with a hierarchical model for between trial heterogeneity to derive an informative prior
- Amount of borrowing – full borrowing/single arm
  - Historical control vs A2311 Secukinumab treatment
- Priors
  - MAP:

$$\theta_{i,\star}|\mu_i,\tau_{i,1} \sim \text{Normal}(\mu_i,\tau_{i,1}^2).$$

priors for the population parameters

$$\mu_i \sim \text{Normal}(0,2^2) \quad \tau_{i,1} \sim \text{Normal}^+(0,1/2^2) \quad \tau_{i,2} \sim \text{Normal}^+(0,1)$$

  - Treatment prior: non-informative

Digital Health technologies as drug development tools

Basel Biostat Society 2022 Spring meeting

Laurent Essioux, Director Data Science, Roche PD-Data Science

23 Mai 2022 | public use

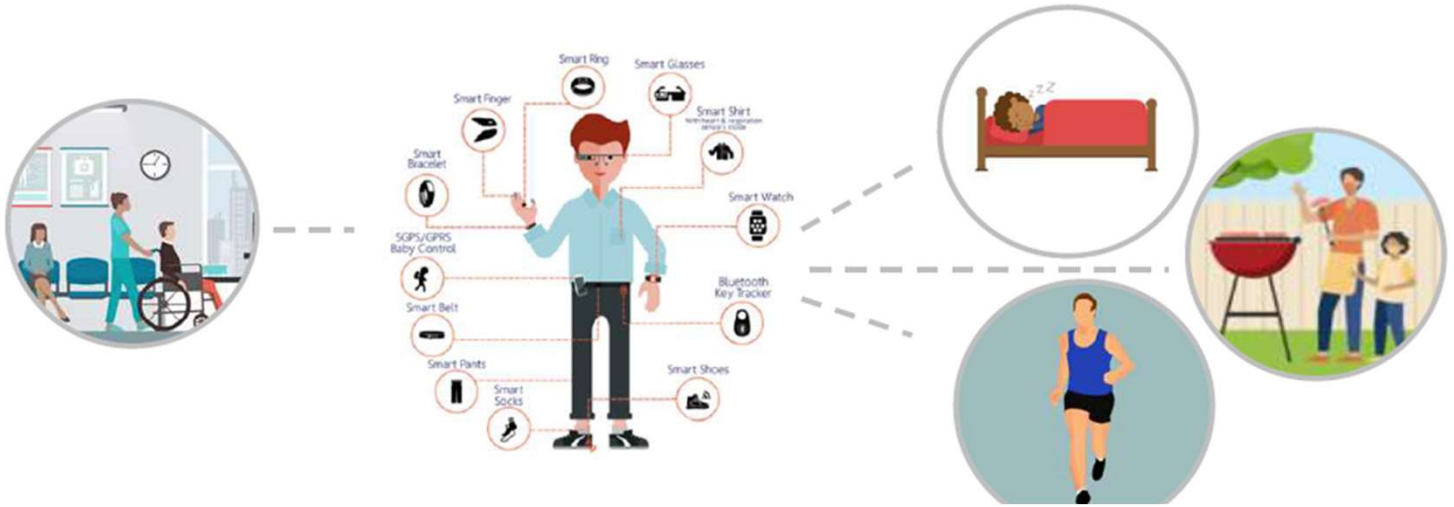
Table of contents

Introduction on DHT as a drug development tool

A quick snapshot on Digital Health technology

"A system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses*

Patient-generated health data (PGHD) collected from digital health technologies (DHTs) allows us to understand patient behavior in the context of their daily lives



Source: www.fda.gov

*Definition from FDA-NIH BEST Glossary. Available at https://www.ncbi.nlm.nih.gov/books/NBK338448/

Promises and challenges of digital measures in clinical development

- **Patient-relevance**
  - Measure actual activities or physical parameter over an “epoch”
  - Address patient-relevant unmet measurement needs
- **Reduced burden**
  - Reduce office visits
  - Increase access to clinical trials
- **Accurate measurement**
  - High sensitivity
  - High signal to noise outcomes

… and the challenges

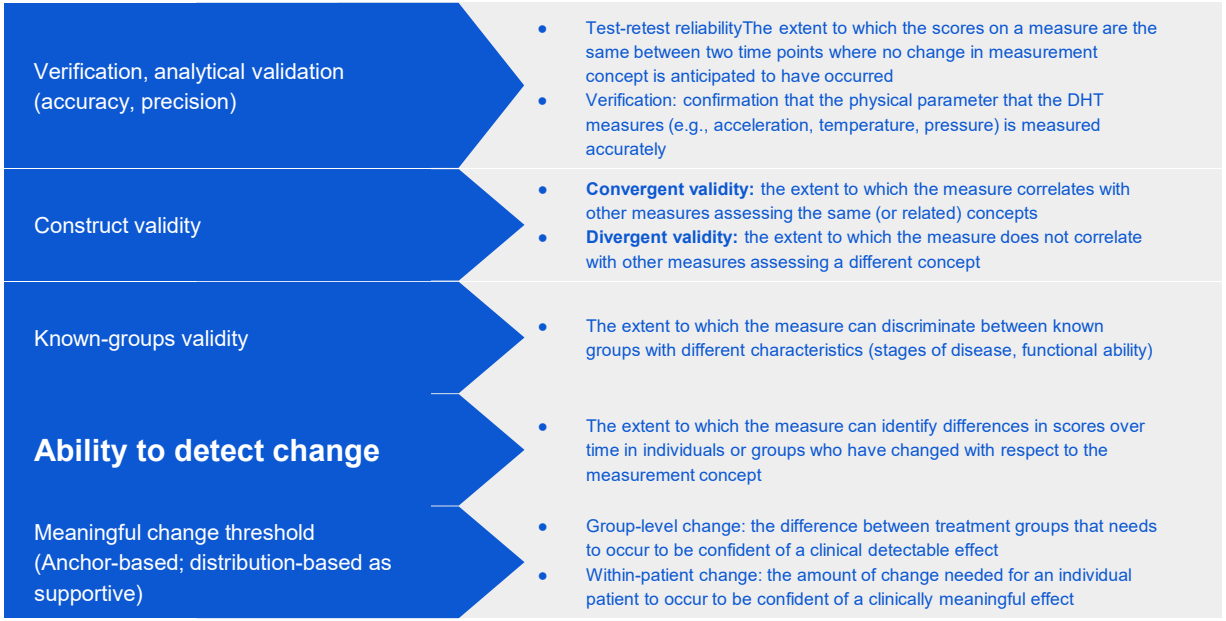
- Meaningfulness
- Data strategy, analytics and validation
- Patient compliance and usability
- Regulatory acceptance
- Ethical issues

FDA Draft DHT Guidance:https://www.fda.gov/media/155022/download

Digital Health Technology as Drug development tool

Objective: Precisely define variable(s) intended to reflect an outcome of interest

- **Concept of interest**: concept meaningful to patients and can be measured by by the DHT.
  - The relationship between the COI and the intended benefit should be defined ; COI assessd by qualitative research (and part have content validity)
- **Context of use**: Circumstances and population of use of the outcome measurement of interest

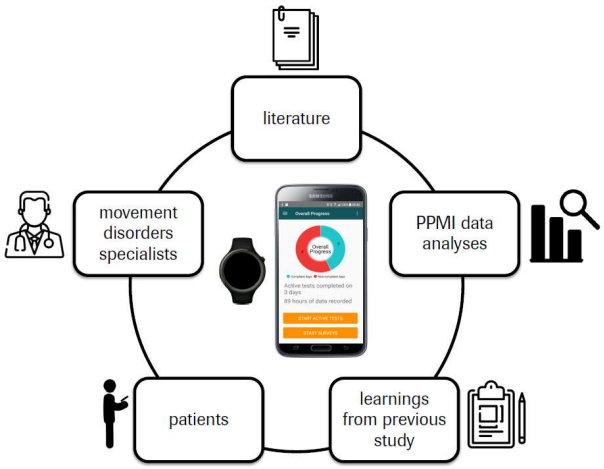


*: A conclusion that the level of validation associated with a DHT is sufficient to support its proposed use.

Building construct and clinical validation of a DHT in Early Parkinson

Roche PD Digital Health Technology Platform v2

Daily remote assessments and passive monitoring with smartphone and smartwatch



ACTIVE TESTS									
Bradykinesia			*Tremor/Bradykinesia*	*Tremor*			*Rigidity/Postural Instability*		*Cognition*
Draw A Shape	Dexterity	Hand Turning	Speech	Phonation	Postural Tremor	Rest Tremor	Balance	U-Turn	Cognitive Test (SDMT)
Bradykinesia Days (Every 2nd Day)			Alternating		Tremor and Stability Days (Every 2nd Day)				Fortnightly

PASSIVE MONITORING		
Bradykinesia and Activities of Daily Living		
Gait	Arm Movement	Mobility & Sociability
Daily	Daily	Daily

Concept of Interest: Ability to perform motor activities in daily life

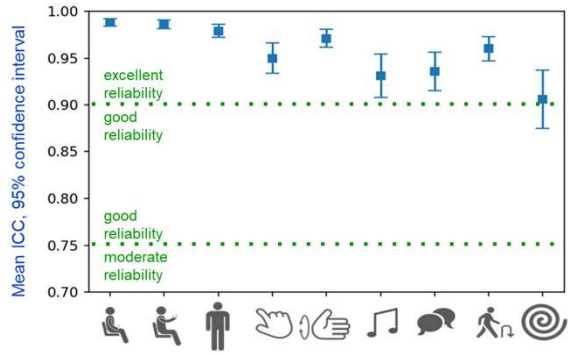
Content validation: In collaboration with Movement disorders expert, patients, and existing tools

Context of Use: To detect treatment effect in Parkinson's disease clinical trials

Analytical and Construct validation and usability Roche PD Digital Health Technology Platform v1 and v2

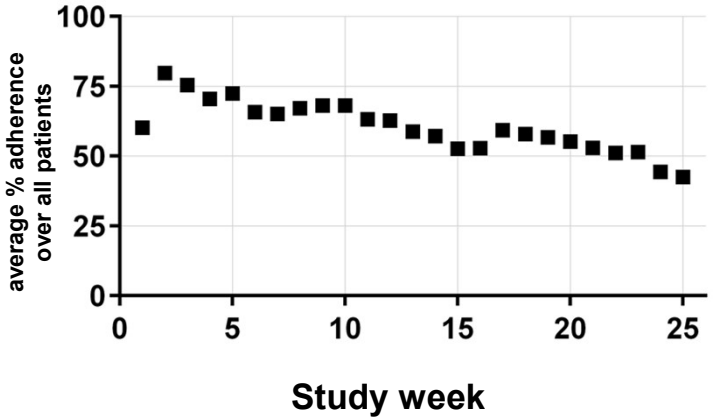
Analytical validation

Intra-class coefficient in aggregated data



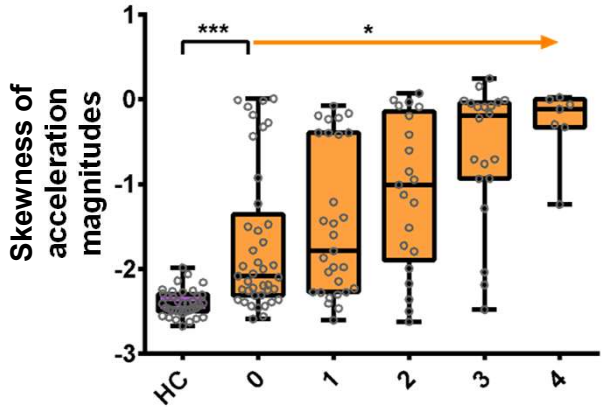
Adherence → Usability

Active Tests adherence over time



Construct validation

E.g. Rest tremor scores



Constancy of Rest Tremor (MDS-UPDRS 3.18)

Lipsmeier, F. *et al.* Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial: Remote PD Testing with Smartphones. *Movement Disorders* (2018). doi:10.1002/mds.27376

Lipsmeier et al (under review) https://www.medrxiv.org/content/10.1101/2021.10.07.21264414v1

PASADENA Phase II trial

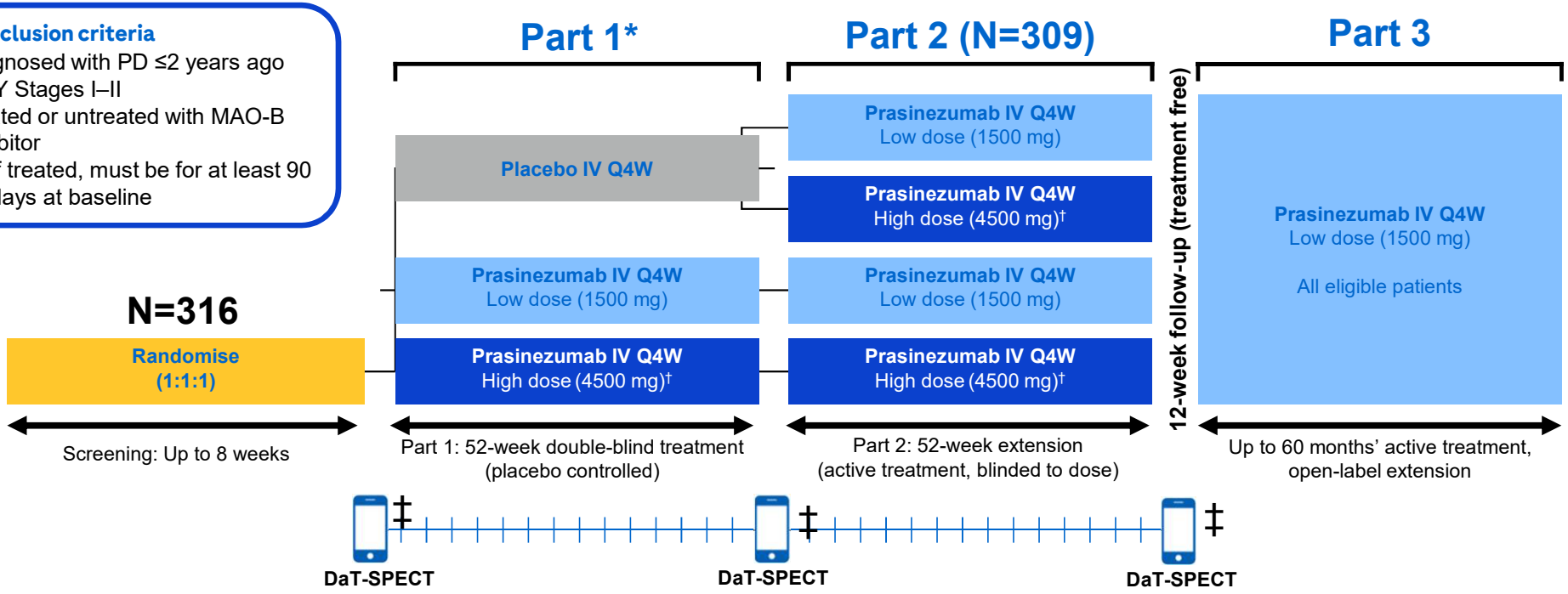
A multicentre, randomized, double blind, placebo-controlled study evaluating efficacy of prasinezumab over 52 weeks in participants with early PD

Recruitment complete across 59 sites in the US, Austria, France, Germany and Spain

PASADENA study design

Key inclusion criteria

- diagnosed with PD ≤2 years ago
- H&Y Stages I–II
- treated or untreated with MAO-B inhibitor
  - if treated, must be for at least 90 days at baseline



DaT-SPECT, dopamine transporter single-photon emission computed tomography; IV, intravenous; Q4W, every four weeks.
* COVID-19 did not affect assessments during PASADENA Part 1 as these were completed before the pandemic. † High dose = 3500 mg for body weight <65 kg; 4500 mg for body weight ≥65 kg.
‡ Digital biomarkers (smartphone and wrist-worn wearable assessments).

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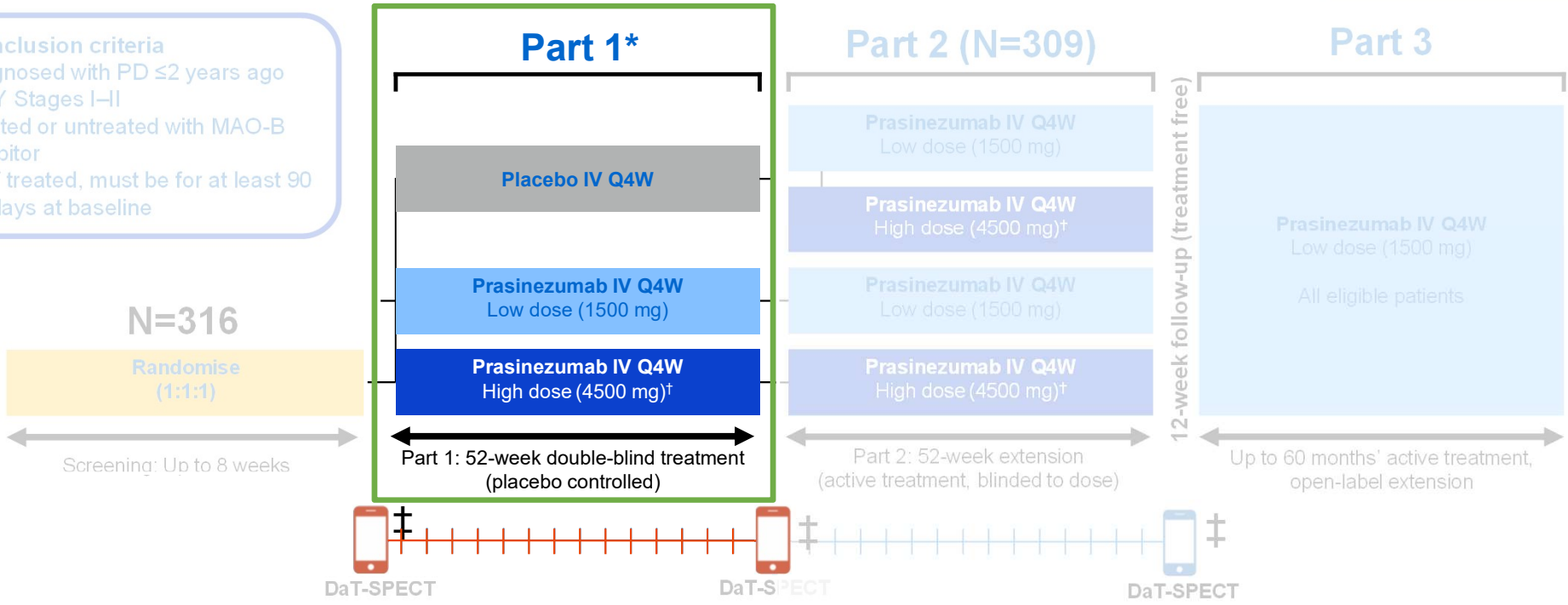

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Taylor et al. ADPD 2022

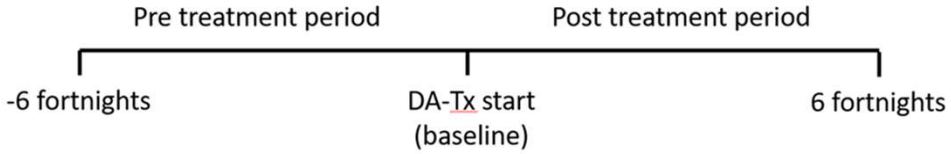
Pre-selected digital outcome assessments – Prior to study read-out!

Category	Source**	Feature	Association with disease***
Bradykinesia	Speeded tapping test	Variability inter-tapping time, L*	+
		Variability inter-tapping time, M*	+
	Hand turning test	Maximum speed, L	-
		Maximum speed, M	-
	Arm movement power (non gait)	Power of gesture –movement vivavcity, in non-walking periods	-
	Draw-a-shape	Spiral celerity (accuracy by time), L	-
		Spiral celerity (accuracy by time), M	-
Gait, balance	U-turn test	Median turn speed	+
	Passive turning	Median turn speed	+
	Balance test	Jerk (rate of change of acceleration with time)	-
Tremor	Postural tremor test	Median squared energy, L	+
		Median squared energy, M	+
	Rest tremor test	Median squared energy, L	+
		Median squared energy, M	+
Speech	Free speech test	Mel frequency cepstrum 2 (Monotonicity indicator)	-
	Sustained phonation test	Voice jitter (deviation from periodicity of periodic voice signal)	+
Cognition	SDMT	Number correct answers	-

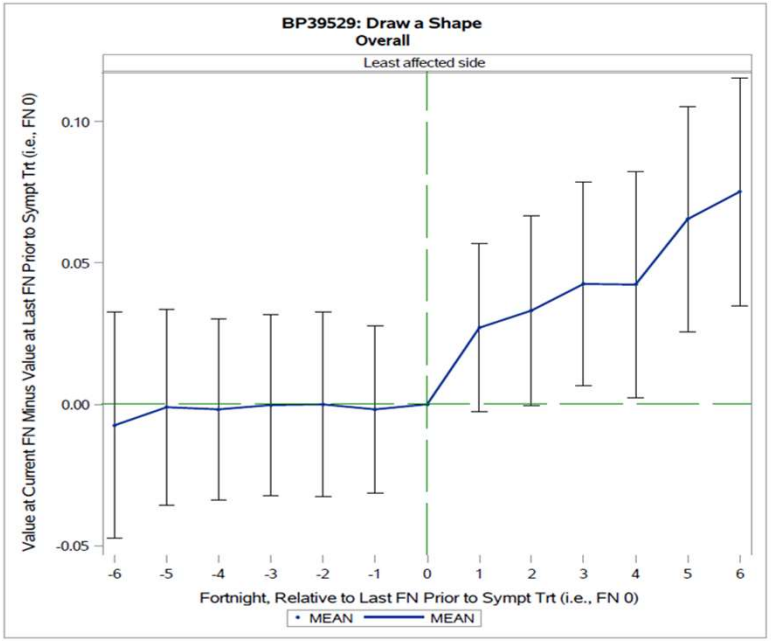
*: L: Least affected side, M: Most affected side; **: Orange: Active test; Blue: Passive monitoring; ***: directionality of association from the cross-sectional correlation and the content validation

Sensitivity of digital features to start of dopaminergic treatment start

- Analysis population
  - Subset ITT population to patients with digital measurements starting dopaminergic treatment during Part I: N=114
- Feature analysis derivations
  - Each digital features outcomes median-aggregated by 2-weeks period (fortnight), log-transformed
    - Missing if less than 3 measurements
- Follow-up period
  - Consider seven fortnights before start of dopaminergic treatment and 6 fortnights after start
  - Consider the fortnight before start as the baseline



- Stat analysis strategy
  - MMRM model of change from "baseline", with fixed effect: Baseline, treatment arm, and fortnight
  - Unstructured variance covariance matrix
  - Null hypothesis: equality of fortnight means between period



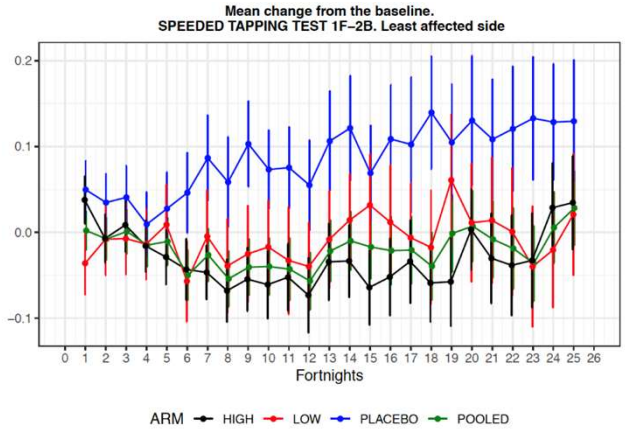
Sensitivity to change of digital feature to dopaminergic treatment start

Category	Source**	Feature	Association with disease***	Effect (se)	pvalue
Bradykinesia	Speeded tapping test	Variability inter-tapping time, L*	+	-0.029 (0.014)	<0.05
		Variability inter-tapping time, M*	+	-0.051 (0.017)	<0.05
	Hand turning test	Maximum speed, L	-	0.006 (0.008)	
		Maximum speed, M	-	0.026 (0.008)	<0.01
	Arm movement power (non gait)	Power of gesture	-	0.088 (0.036)	<0.05
	Draw-a-shape	Spiral celerity, L	-	0.035 (0.012)	<0.01
		Spiral celerity. M	-	0.052 (0.017)	<0.001
Gait, balance	U-turn test	Median turn speed	-	0.019 (0.006)	<0.001
	Passive turning	Median turn speed	-	0.019 (0.006)	<0.01
	Balance test	Jerk	-	-0.038 (0.04)	
Tremor	Postural tremor test	Median squared energy, L	+	-0.046 (0.026)	
		Median squared energy, M	+	-0.060 (0.04)	
	Rest tremor test	Median squared energy, L	+	0.013 (0.04)	
		Median squared energy, M	+	-0.074 (0.042)	
Speech	Free speech test	Mel frequency cepstrum 2	-	-0.025 (0.011)	<0.05
	Sustained phonation test	Voice jitter	+	-0.007 (0.014)	
Cognition	SDMT	Number correct answers	-	0.034 (0.005)	<0.001

*: L: Least affected side, M: Most affected side; **: Orange: Active test; Blue: Passive monitoring; ***: directionality of association from the cross-sectional correlation and the content validation

Statistical analysis of digital features in Pasadena Part I (I)

- **Analysis population and arms**
  - ITT population with digital data at baseline: N=315 at baseline (out of 316)
  - Prasinezumab treatment groups combined
- **Follow-up period: 52 weeks (26 fornights)**
  - Data censored at the start of symptomatic treatment (hypothetical strategy)
- **Feature derivation**
  - Digital features outcomes median-aggregated by 2-weeks period (fortnight), log-transformed



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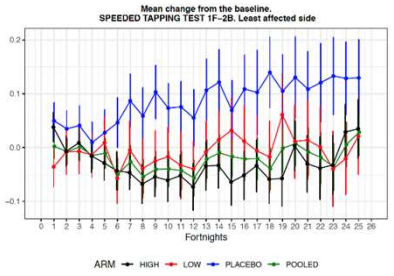
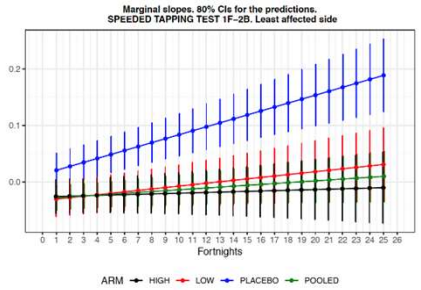
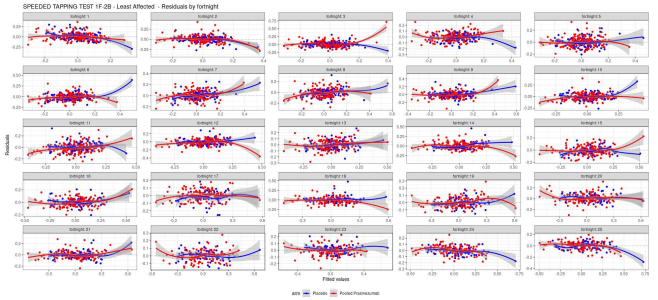
Statistical analysis of digital features in Pasadena Part I (II)

- Dependent variable: Change from baseline of digital feature
- Covariates: baseline MAO-Bi therapy Yes/No; Age; Sex; baseline DaT-SPECT Specific Binding Ratio in contralateral putamen, baseline feature, treatment arm, **treatment by fornight interaction**
- Linear mixed effect model with random intercept and slope, with AR(1) auto-correlation
  - Inspection of residuals to asses linear fit and distribution across factors (fornights, fitted values)
  - If good model fit (visual inspection!). Test of absence of arm by fornight interaction
- In case of lack of fit, non-normality
  - MMRM model. UN Var-Covar matrix, same fixed effects
  - Hypothesis testing: Equality of change from baseline at week 52 (fornight 26)







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Sensitivity to change of digital feature to dopaminergic treatment start

Category	Source**	Feature	Association with disease***	p-value	LME/MMRM
Bradykinesia	Speeded tapping test	Variability inter-tapping time, L*	+	0.02	LME
		Variability inter-tapping time, M*	+	0.07	LME
	Hand turning test	Maximum speed, L	-	-	MMRM
		Maximum speed, M	-	0.06	MMRM
	Arm movement power (non gait)	Power of gesture	-	0.02	MMRM
	Draw-a-shape	Spiral celerity, L	-	0.11	LME
		Spiral celerity. M	-	-	MMRM
Gait, balance	U-turn test	Median turn speed	-	0.17	LME
	Passive turning	Median turn speed	-	-	MMRM
	Balance test	Jerk	-	-	LME
Tremor	Postural tremor test	Median squared energy, L	+	-	MMRM
		Median squared energy, M	+	-	LME
	Rest tremor test	Median squared energy, L	+	-	MMRM
		Median squared energy, M	+	-	LME
Speech	Free speech test	Mel frequency cepstrum 2	-	-	LME
	Sustained phonation test	Voice jitter	+	-	LME
Cognition	SDMT	Number correct answers	-	-	MMRM

*: L: Least affected side, M: Most affected side; **: Orange: Active test; Blue: Passive monitoring; ***: directionality of association from the cross-sectional correlation and the content validation

Building the clinical validation of the Roche PD mobile app

- Digital features in the motor domains are sensitive to dopaminergic treatment start
  - Helpful to understand the digital features behaviors
- Digital features recapitulates the Prasinezumab treatment effect
  - Prasinezumab reduced clinical decline in motor signs at Week 52 compared with placebo based on MDS-UPDRS Part III score
- Our next step: towards development of an endpoint
  - Establish the association with clinical endpoints and longitudinal association
    - Definition of “meaningful” events
  - Using natural history studies/observational cohort

Can it be useful in clinical development already?

Use of PD Roche Mobile application v2 as an early clinical development tool: Sample size calculation of a proof of mechanism Study – hypothetical example

- Context
  - Team is considering an initial phase II trial to test their drug in early PD
  - Trial such as Pasadena is long, could we use the DHT to compute sample size based on digital endpoint for a trial at 4 / 6 months?
  - MinTPP is 25% reduction of slope
- Approach
  - Use Pasadena Data to base simulation
  - Use MD-UPDRS part III as an alternative (No surrogacy established)
  - Use a score spanning across bradykinesia and gait features (weighted average across digital features) as the "digital endpoint"
  - Sample size at MDD (power = 50%, alpha=0.2)

Sample size per arm at "MDD"

Follow-duration	Sample size / Arm
4 months	170
6 months	83

Fortnight	Fraction missing data
0	0
4	12
8 (4 months)	14
12 (6 months)	20

Conclusions

- Potential of DHT as drug development tools !
  - Careful rationale and rigorous approach to build evidence on the clinical validation of the tool is needed
- Multiple use of DHT in clinical development
  - Along the way of the endpoint development, DHT can be a useful tool for early clinical development
- Stats approaches need to be tailored to the nature of the data
  - Longitudinal approaches !
  - Multivariate score construction
  - Handling missing data (ref)
  - Trajectory and “event” definition
  - Inferring minimal clinical important difference (MCID)
  - Learning and practice effect
  - …..

Acknowledgments

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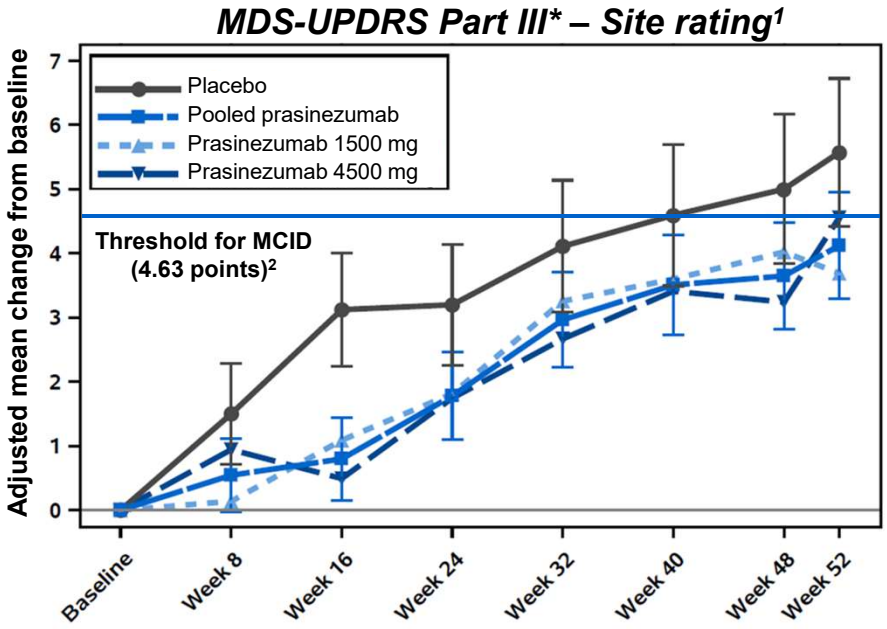
Pharma Research and Early development

- Kirsten I. Taylor, Michael Lindemann, Florian Lipsmeier, Ekaterina Volkova-Volkmar, Ben Van Lier, Gennaro Pagano…

PD-Data Science

- Marzia Sclesi, Judith Anzures Cabrera, Daria Rukina, Dave Summers, Annabelle Monnet

Prasinezumab reduced clinical decline in motor signs at Week 52 compared with placebo based on MDS-UPDRS Part III score



Pooled: –1.44, 80% CI=(–2.84, –0.05); **–25.9%**
Prasinezumab 1500 mg: –1.88, 80% CI=(–3.49, –0.27); **–33.8%**
Prasinezumab 4500 mg: –1.02, 80% CI=(–2.64, 0.61); **–18.2%**

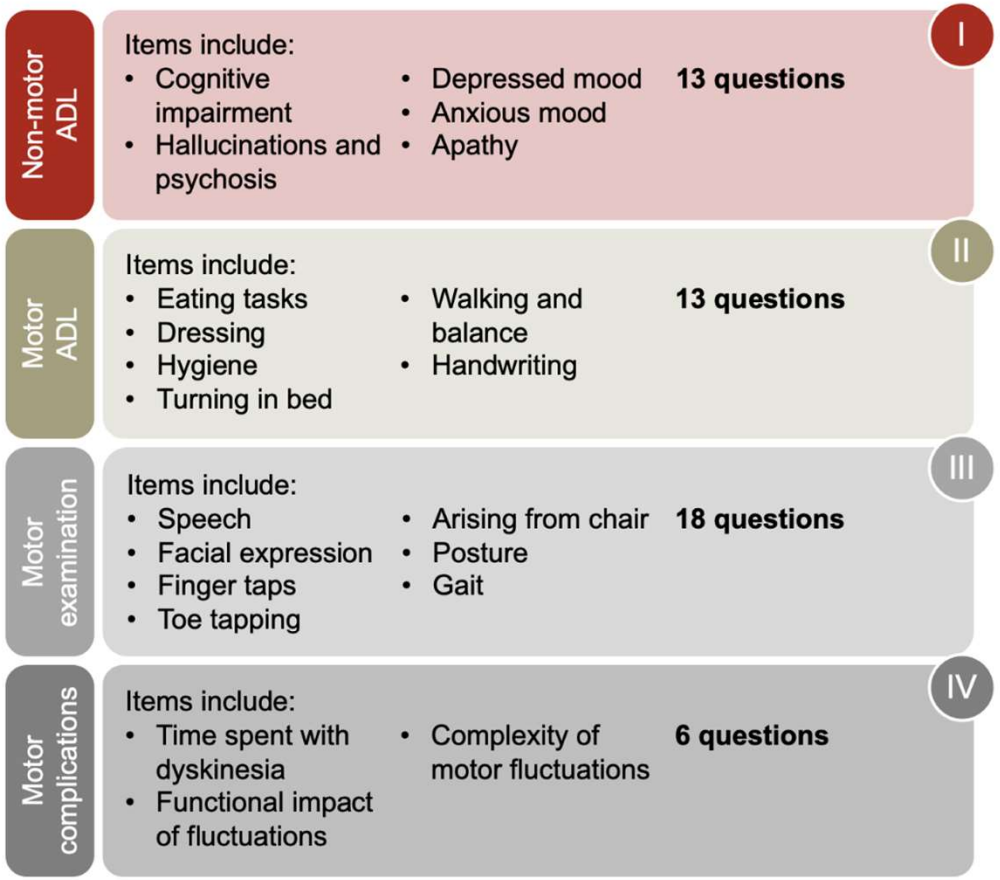
* Patients who started symptomatic PD treatment contribute until the last visit before symptomatic PD treatment is started. Bars represent 80% CI. Estimates are based on an MMRM with the following covariates: MAO-B inhibitor at baseline (yes/no), treatment, week, age (<60 vs. ≥60), sex, DaT-SPECT putamen binding ratio (contralateral to most clinically affected side), baseline MDS-UPDRS corresponding endpoint. Pooled-dose analysis is a pre-specified exploratory analysis. 4500 mg for participants ≥65 kg; 3500 mg for participants <65 kg. Data readout correct based on snapshot from January 2020.

CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; MAO-B, monoamine oxidase B; MCID, minimal clinically important difference; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; MMRM, mixed-effect model repeated measures; PD, Parkinson's disease.

1. Pagano G, et al. *Eur J Neurol.* 2021; 21:Suppl 1 (OPR-104). Presented at virtual EAN 2021; 2. Pagano G, et al. *N Engl J Med.* 2021; In submission.

MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

- Measures disease progression[1,2]
- Combination of 4 sections:[1,2]
  - I: Non-motor aspects of experiences of daily living
  - II: Motor aspects of experiences of daily living
  - III: Motor examination
  - IV: Motor complications
- Items are rated on a 5-point scale:[1,2]
  - 0 = normal (no impairment/disability)
  - 1 = slight
  - 2 = mild
  - 3 = moderate
  - 4 = severe (maximum impairment/ disability)



MDS=Movement Disorder Society

1. Goetz et al. Mov Disord 2008;23(15):2129–2170; 2. Goetz et al. Mov Disord 2007;22(1):41–47

Lundbeck Institute Campus

Roche

Doing now what patients need next

BBS assembly

May 24, 2022

Agenda

1. Report of the President (Uli)
2. Report of the treasurer (Fred)
3. Elections
   - President (Uli available for reelection)
   - Treasurer (Fred available for reelection)
   - New board members
4. General questions

BBS – What are new activities?

Overall we continue doing very well

- Seminars
  - Continued with the program, just now virtual
  - Virtually we reached out to many more people than before
  - Made BBS well known in Biometrics in Europe and the world
- Training sessions
  - Continued with the training and have now about 3-4 trainings every year
  - Trainings in the last 2 years have been virtual with very high attendance again from global
- We continue doing things together with others, especially EFSPI

BBS – What is new in BBS?

- Changes in BBS
  - We basically changed our name from «Basel Biometrische Sektion» to Basel Biometric Society – A section of the ROeS»
  - Logo and statutes were changed accordingly
  - New website (thanks to Kaspar!)
- BBS board fairly stable with a continued great collaboration through the pandemic
  - Everyone is engaged
  - A lot of ideas for seminars etc. come out of the board
  - There are always volunteers in the board to take on work for BBS
  - This makes BBS currently very successful!
- Important however that people outside the board should also get engaged in BBS activities

BBS – What is new for collaborations?

- Great collaboration and joint meetings with BES
  - BES is an important «sister» of the BBS for epidemiologists
  - But we have really healthy great collaboration for the benefit of all!
- We benefit a lot from EFSPI and continue the engagement
  - EFSPI regulatory statistics workshop in September in Basel again face to face (Biozentrum), then perhaps alternating with Amsterdam
  - Have regular joint meetings with EFSPI (around 2-3 every year)
  - Ensures that we are well connected with others
  - Marisa and I are still on the EFSPI council
- We are engaged with ROeS
  - We are very well connected with ROeS, being a section of it
  - Moved also ROeS admin office 2019 from Bern to Basel. Dominik is the treasurer of the ROeS
  - Frank Bretz elected as new ROeS president

BBS – Important other topics

- We managed overall well the pandemic. But this first spring seminar is something really special!
- We need to continue getting also younger colleagues engaged. Here we are not yet there...
- We will do more training together with EFSPI and other member organizations, basically moving it to something like a European training academy
- CEN 2023 in September in Basel!
  - This will be a major event
  - Early September 2023 at the Biozemtrum
  - BBS heavily ebgaged in the organization of the meeting as the meeting is a great opportunity for us in Basel

Report of the Treasurer 2020 - 2022
Balance of 1. November 2019: CHF 5’863.57

Major Expenses	Main Incoming Revenues	Date (Month)	Amount
	Fees received from Novartis for BBS Causal inference course 2019	November 2019	5’000.00
Expenses for BBS predictive modelling seminar		November 2019	(678.77)
Expenses for Network meta-analysis seminar		February 2020	(1’404.93)
EFSPI membership dues 2020		May 2020	(1,338.59)
	Fees received from J&J/Actelion for BBS Causal inference course 2019	June 2020	2’000.00
EFSPI membership dues 2021		February 2021	(1,339.84)
BBS Council working lunch 2021		August 2021	(495.40)
EFSPI membership dues 2022		March 2022	(1,309.04)

Current Balance 1. May 2022: CHF 6’091.60

Elections

1. President.

Candidate: Uli Burger

1. Treasurer

Candidate: Fred Sorensen

Elections

3. Board members

   Amanda Ross and Simon Wandel will leave the board

   THANKS TO BOTH!!!!

New members:

Olympia Papachristofi, Novartis

Brian Hennessy, Janssen

Tracy Glass, University Basel and Swiss Tropical institute

Thank You and Discussion