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Prader-Willi Syndrome
Organisation

Overview of the Clinical Trials Process

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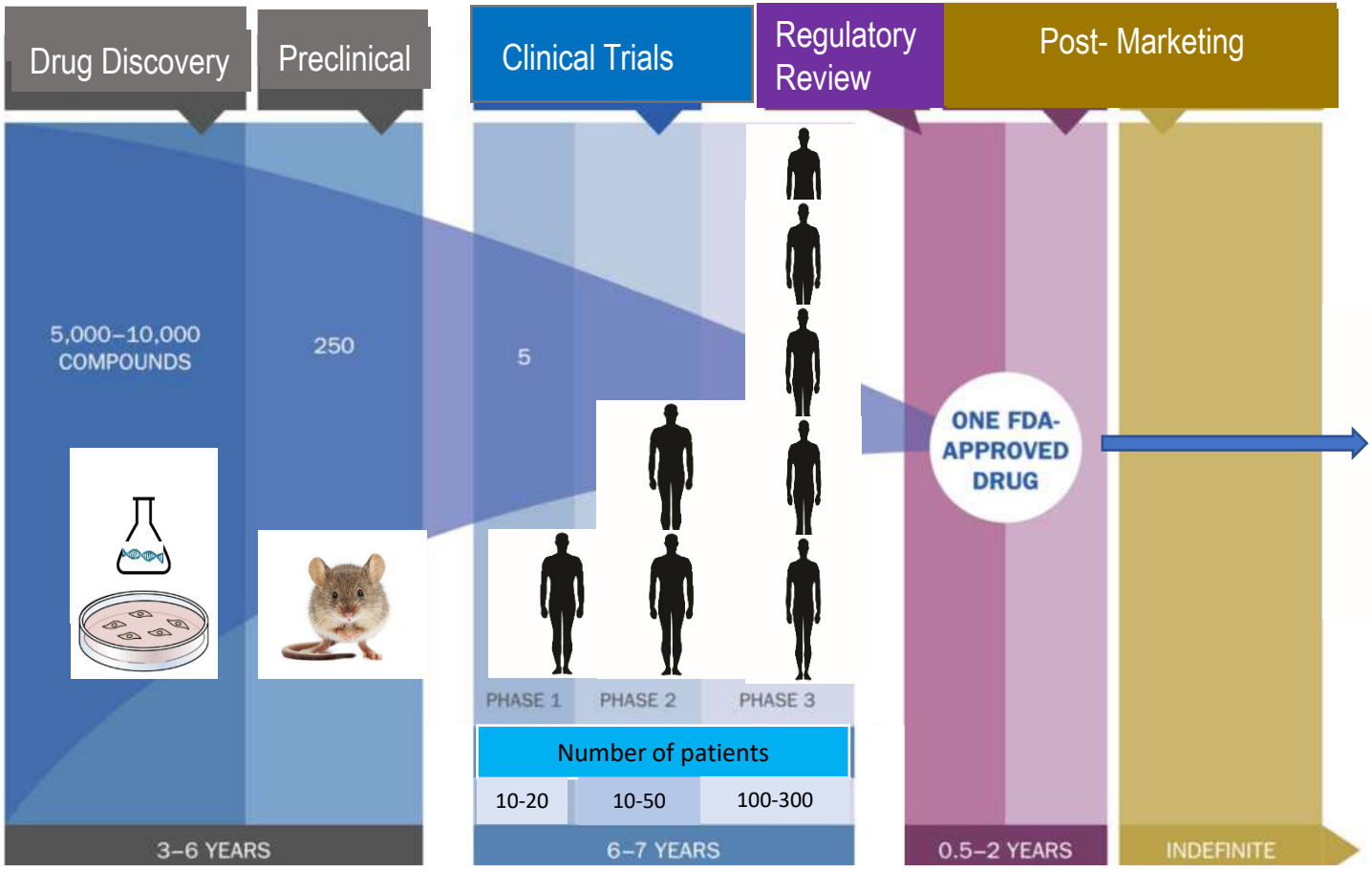
Drug development process



New target-drug identification Laboratory → **Safety Efficacy** Animal → **IND Submission** → **Dose, Safety, Efficacy** Humans → **Market Authorization** → **Drug approved** → **Surveillance & Drug price & Reimbursement** → **Drug access to patients**

Drug: A substance intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.

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Drug development is long, costly, inefficient

It takes ~ **10-15 years** to develop a new drug

It costs **~$ 2,600 million** (50-70% for rare diseases) to develop a new drug

55%-90% of drugs entering phase 1 clinical trial will fail*

*DiMasi et al., J. Health Econ, 2016; Hwang et al, JAMA, 2016

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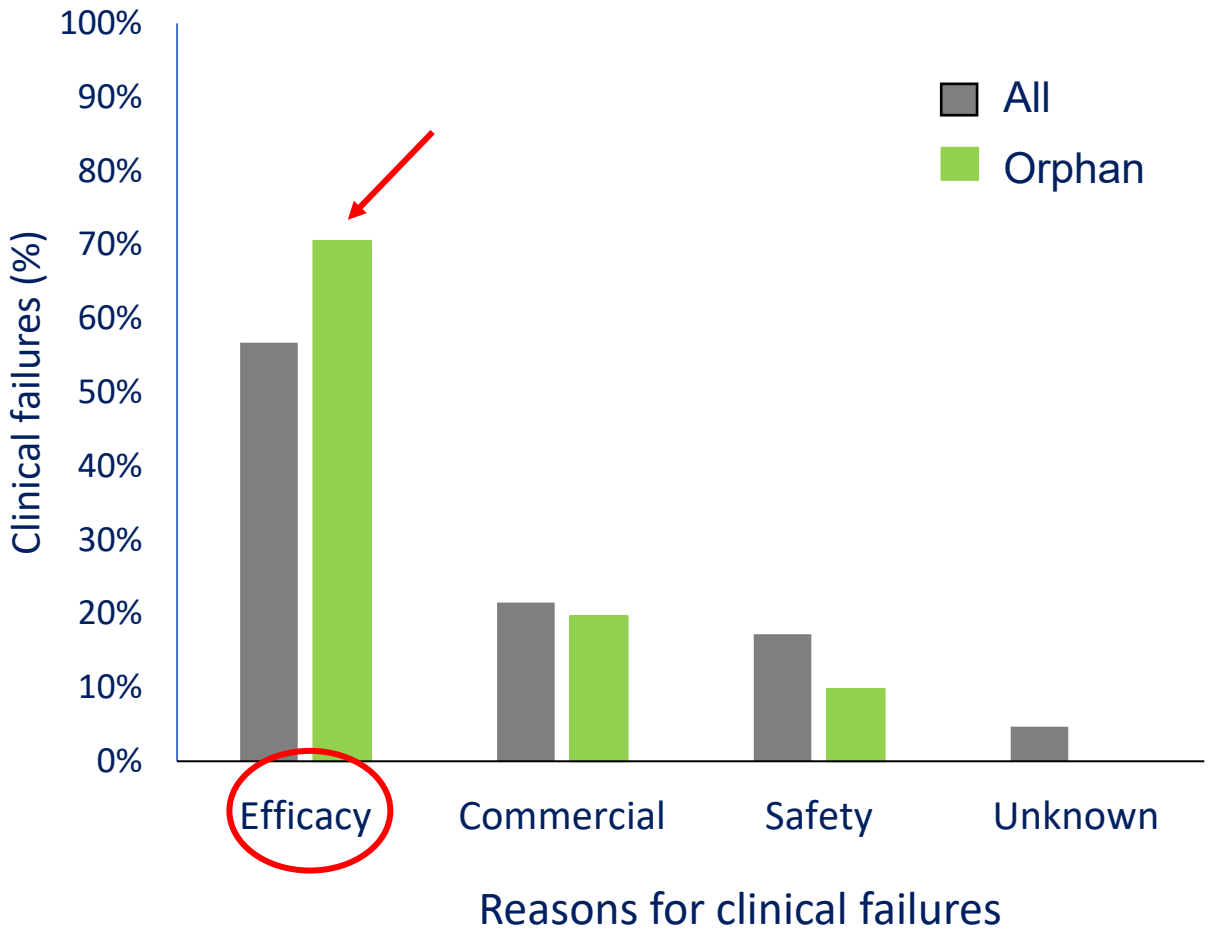
Lack of efficacy is the main reason for clinical failures



Hwang et al, JAMA, 2016

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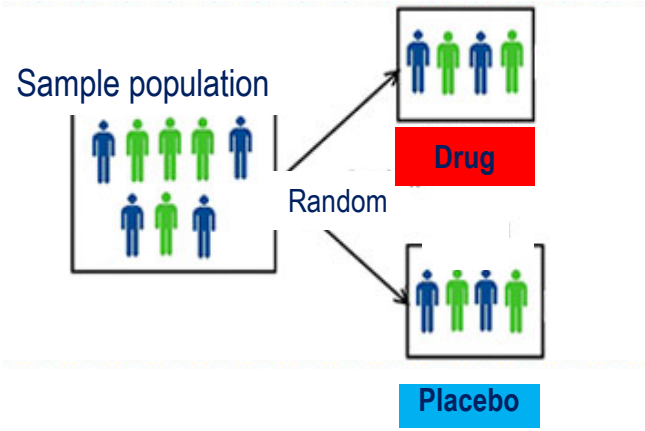
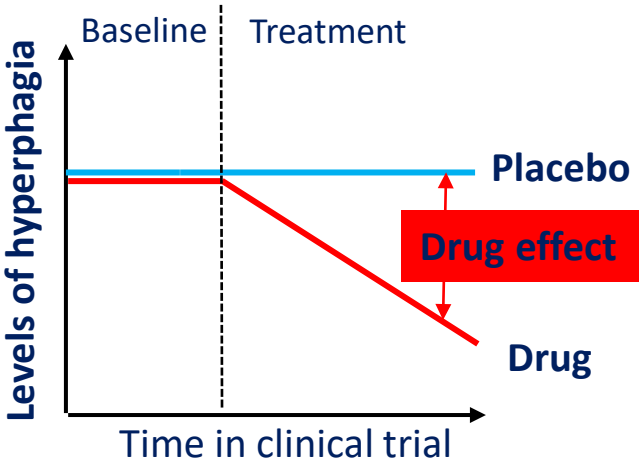
Clinical trial concepts: definition

CONCEPTS	DEFINITION
Randomized placebo-controlled clinical trial	Trial has been designed well enough so as to be able **"to distinguish the effect of a drug from other influences**, such as spontaneous change…, placebo effect, or biased observation"
Placebo	A **placebo** is an inactive **drug** or treatment used in a **clinical trial**.
Open label	A trial in which **no blinding** is used and all parties are aware of the treatment groups is called open label or unblinded
Primary endpoint	Primary outcome measured by a clinical trial to assess the effect of a drug. Primary endpoints are required for **approval by regulatory agency**.
Secondary endpoint(s)	Secondary endpoints are measures that may **support** the primary endpoints or demonstrate **additional clinical effects**.





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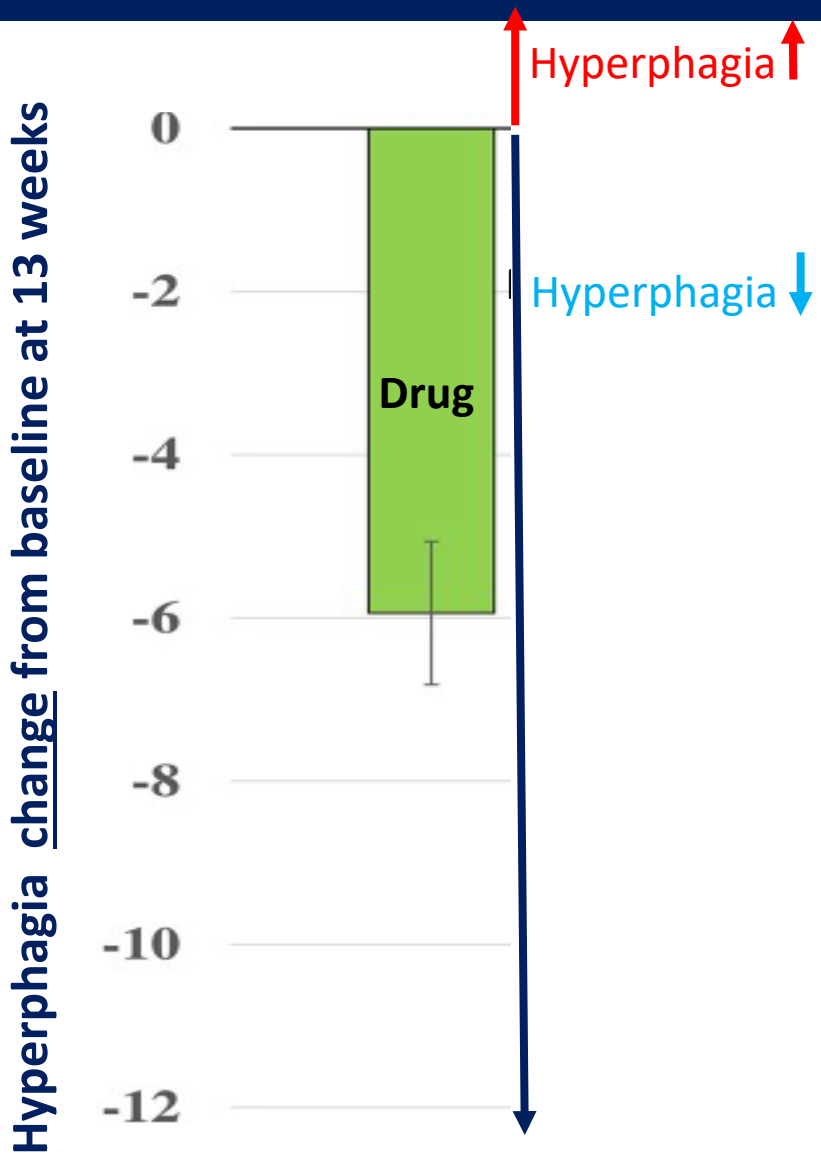
Why placebo-controlled trials are important?



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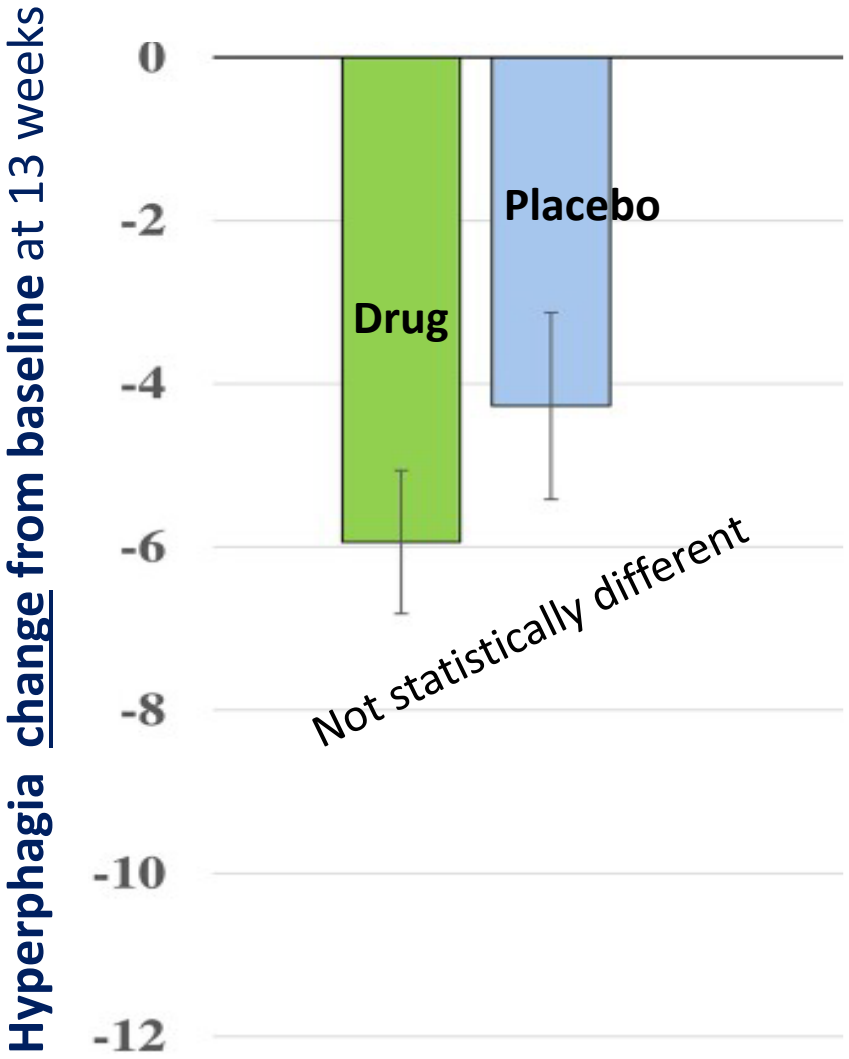

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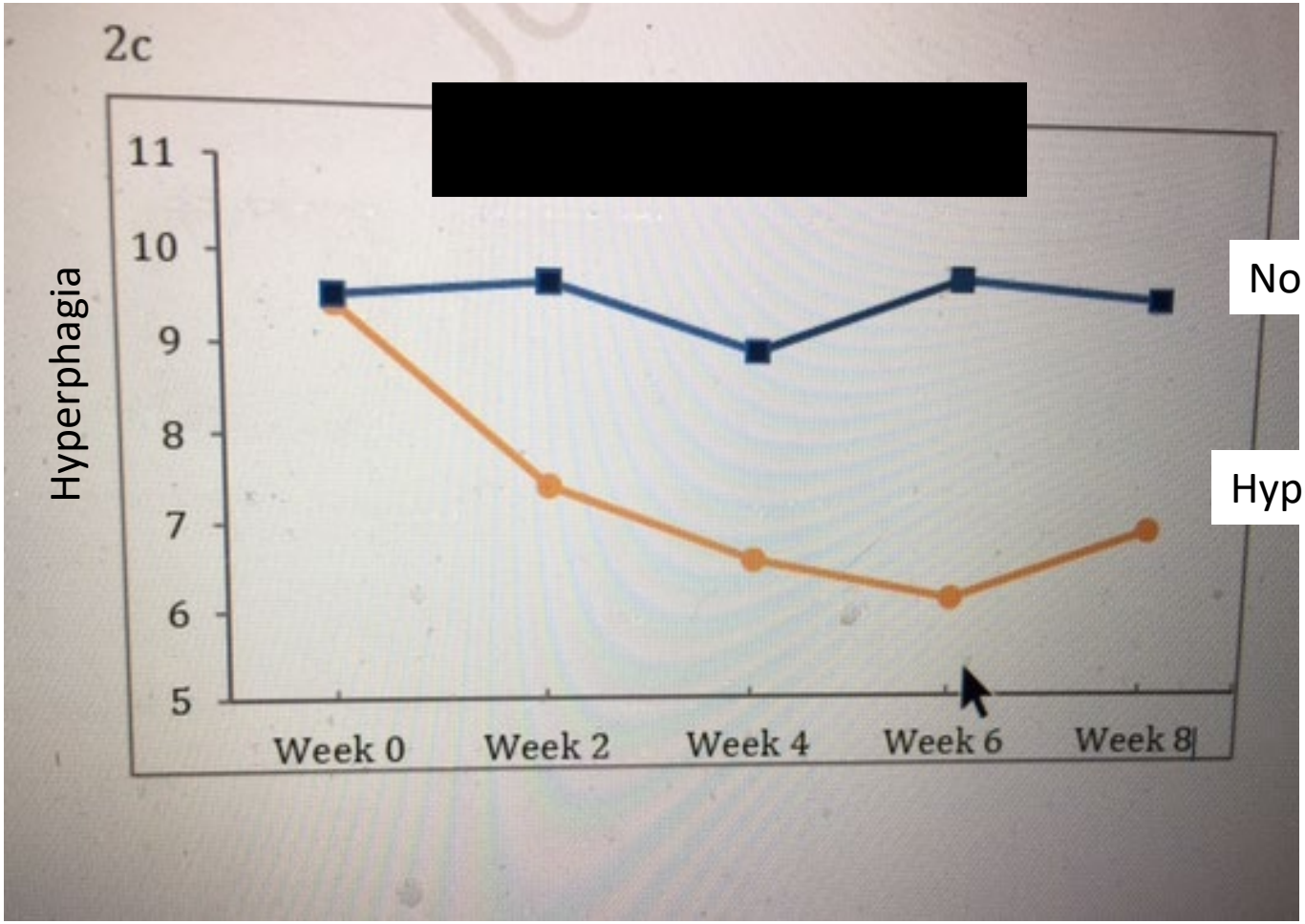

No effect

Hyperphagia ↘

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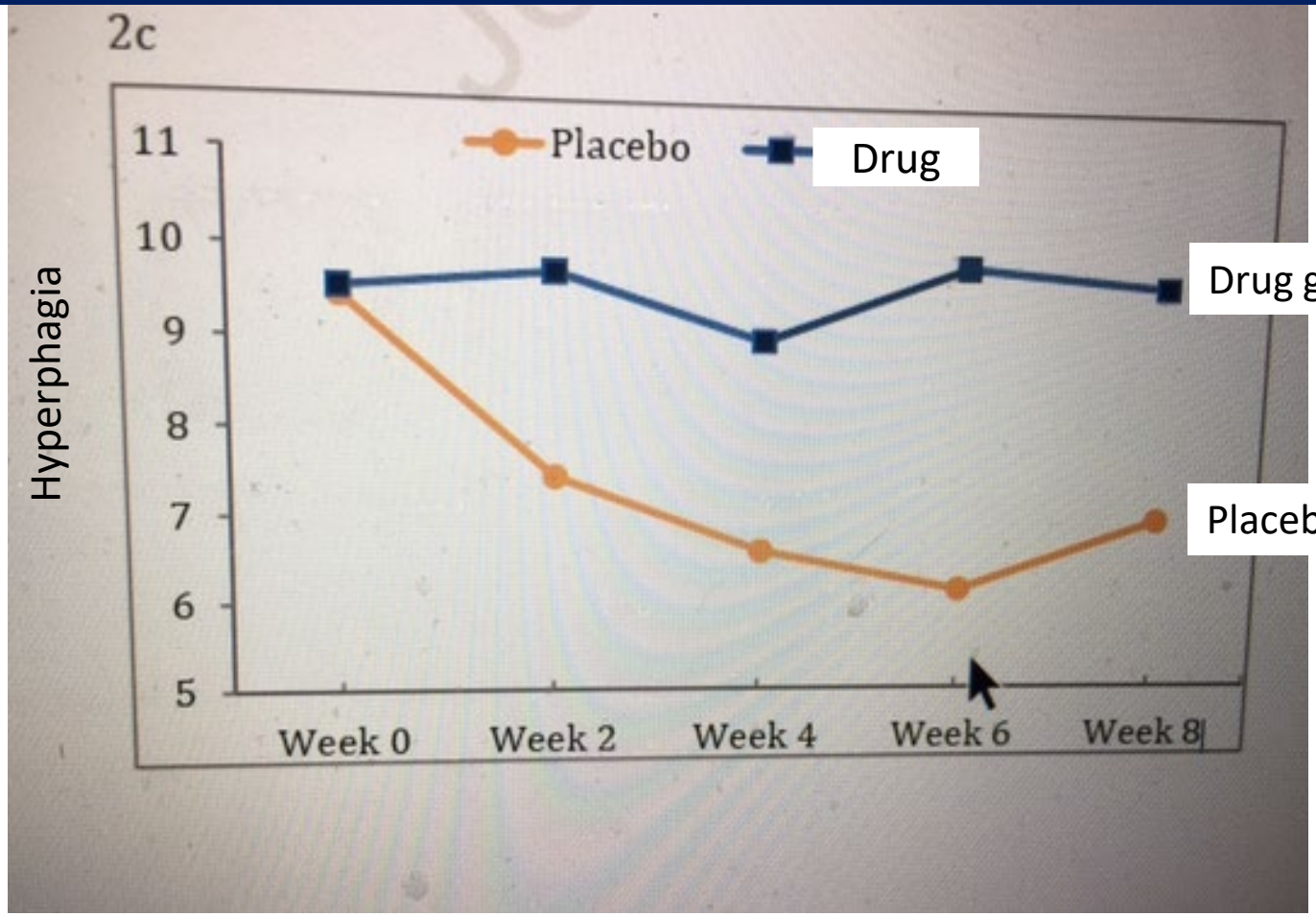
Why placebo-controlled trials are important?



Drug group

Placebo group!

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The critical role of patients and caregivers in clinical trials

- Patient-centric design of clinical trials
- Representativity (age, symptoms, ethnicity, socio-economic) of the community in trials
- Design of meaningful clinical trial endpoints
- Gather evidence-based data on what matters to the community
- Involvement in the post-marketing period

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Thank you!

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Additional Slides

Clinical trials phases for new drugs

Drug tested

Drug approved

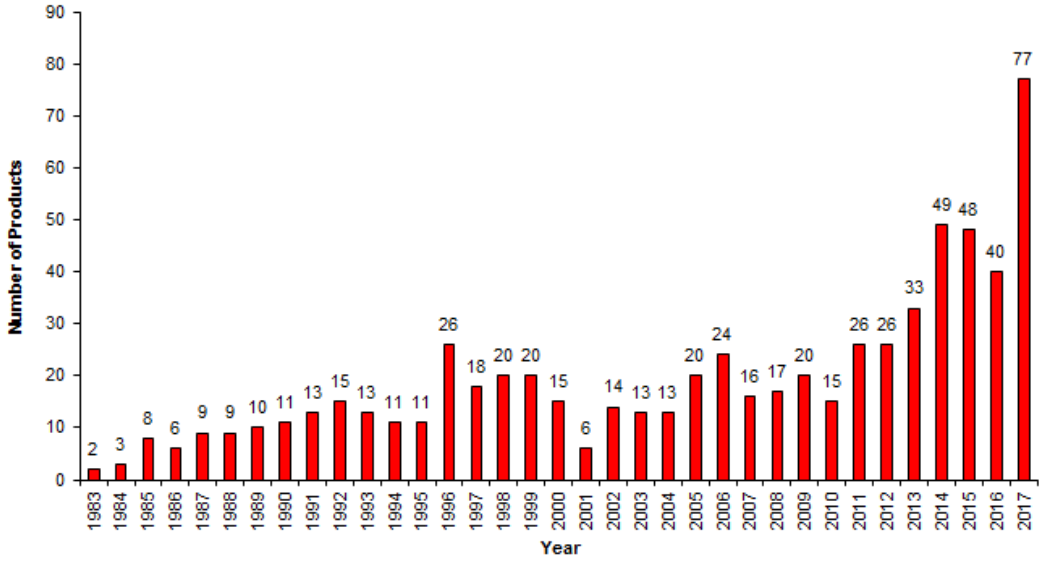
Phase 1	Phase 2	Phase 3	Phase 4
SAFETY and DOSE SELECTION	**SAFETY/ EFFICACY**	**EFFICACY/ SAFETY**	**REAL-WORLD EVIDENCE**
10-20 patients	**10-50 patients**	**100-300 patients**	**up to thousands patients**
Short exposure	**Short exposure**	**Longer exposure (2 months-1 year)**	**>1 year**
First study in humans			
Mutiple doses are tested : what is the dose where you see an effect, and where side effects appear?	**Efficacy**: How well drug works?	**Efficacy**: is the drug effective in comparison to placebo, do clinical benefits outweigh the risk?	**Long term effectiveness:** how well the medicine works when used in the real-world
Safety: How well is the drug tolerate? Does it distribute to the body? How long does the drug stay in the body?	**Safety**: expand safety assessments on the highest dose tolerated	**Must reach predetermined "endpoints"**	Collect additional information about side-effects and safety, long-term risks and benefits

Regulatory incentives for orphan drug development

	United States	Japan	Australia	European Union
Legislation date	1983 **Orphan Drug Act**	1993	1997/8	2000
Prevalence*	Fewer than 200,000 (6.25 per 10,000)	Fewer than 50,000 (4 per 10,000)	Fewer than 2,000 (1.1 per 10,000)	Fewer than 5 per 10,000
Market exclusivity	7 years	Re-examination period extended from 4 to 10 years	None	10 years
Fee waiver	Yes	No	Yes	At least partial

- Protocol assistance
- Tax credits
- Accelerated approval strategies
  (Priority Review, Breakthrough Therapy, Accelerated Approval, Fast Track)

Number of FDA approved orphan products by year



Pushpakom et al., Nature Rev 2018

FOUNDATION FOR PRADER-WILLI RESEARCH

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

1 Understanding the Disease or Condition

A. Natural history of the disease or condition
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

B. Patient subpopulations
- By severity
- By onset
- By comorbidities
- By phenotype

C. Health care environment
- Treatment alternatives
- Clinical care standards
- Health care system perspective

D. Patient/caregiver perspectives
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

2 Conceptualizing Treatment Benefit

A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:
- Survives
- Feels (e.g., symptoms)
- Functions

B. Define context of use (COU) for clinical trial:
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

C. Select clinical outcome assessment (COA) type:
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

3 Selecting/Developing the Outcome Measure

A. Search for existing COA measuring COI in COU:
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

B. Begin COA development
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for COA qualification for use in exploratory studies

C. Complete COA development:
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
http://www.fda.gov/Drugs