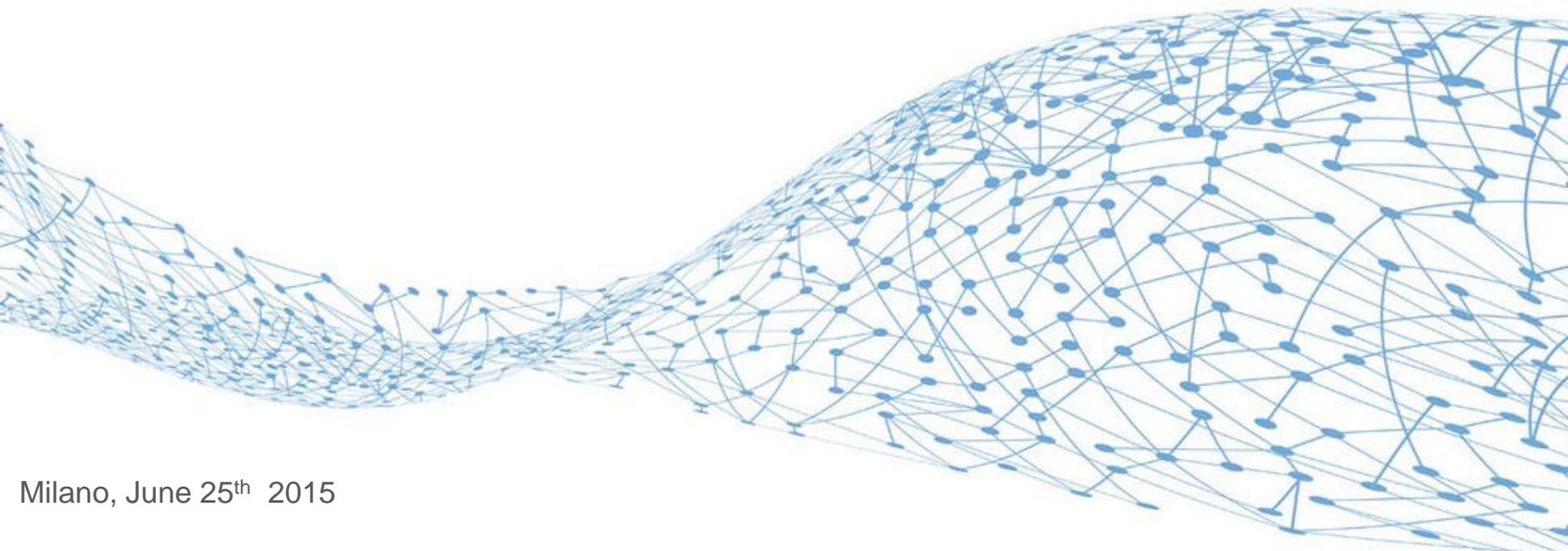
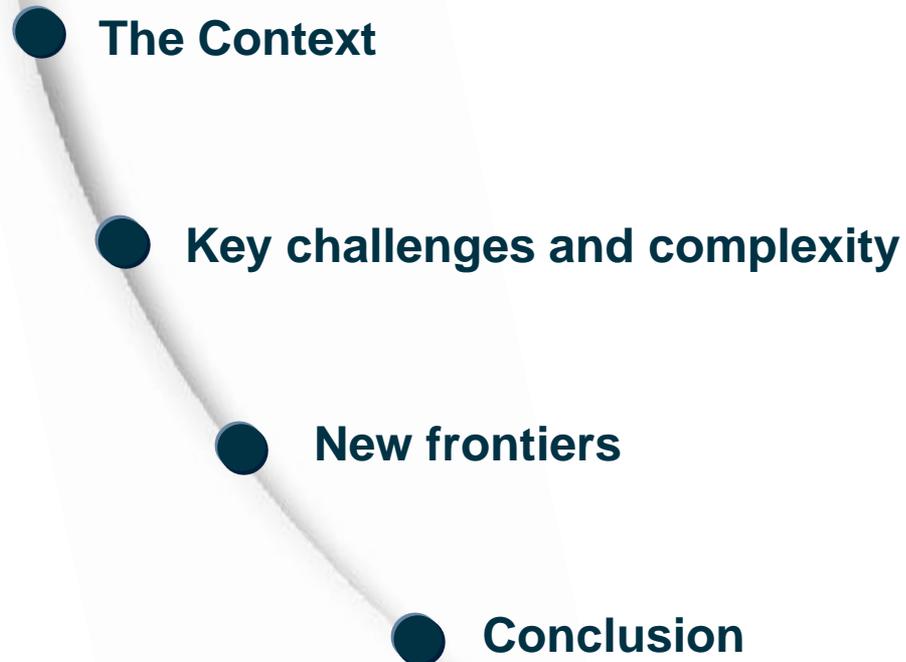


Clinical Research in Neurosciences: challenges and new frontiers

Emanuela Roccato

Country Clinical Operations Therapeutic Area Leader



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- A graphic of a white document with a shadow, tilted slightly to the right. A dark blue curved line runs down the left side of the document, with four dark blue circular markers. To the right of each marker is a text item from the agenda.
- **The Context**
 - **Key challenges and complexity**
 - **New frontiers**
 - **Conclusion**



The Context



Key challenges and complexity



New frontiers



Conclusion

Once upon a time ...



GOOD NIGHT

PATIENTS SLEEP SOUNDLY with non-barbiturate Doriden—0.5 Gm. at bedtime. Onset of action is smooth and gradual (without preliminary excitation). Effect lasts 4 to 8 hours.

Doriden®
chloralhydrate USP

GOOD MORNING

PATIENTS AWAKE ALERT and REFRESHED. Doriden is rapidly metabolized, allows mental freedom with little or no hangover.

CIBA PHARMACEUTICALS

BETTER LIVING through CHEMISTRY

Mother's LITTLE HELPER

Net Wt. 4oz. (112g)

Escape to reality

Librium®

An important aid in the treatment of neurosis.

After the acute sedative has been controlled, Librium provides a gradual and sustained relief of anxiety and tension, and helps to restore the patient's equilibrium.

Librium provides a gradual and sustained relief of anxiety and tension, and helps to restore the patient's equilibrium.

When the patient lashes out against "them"—

THORAZINE®
brand of chlorpromazine

quickly puts an end to his violent outburst

'Thorazine' is especially effective when the psychotic episode is triggered by delusions or hallucinations.

At the outset of treatment, Thorazine's combination of antipsychotic and sedative effects provides both emotional and physical calming. Assaultive or destructive behavior is rapidly controlled.

As therapy continues, the initial sedative effect gradually disappears. But the antipsychotic effect continues, helping to dispel or modify delusions, hallucinations and confusion, while keeping the patient calm and approachable.

SMITH KLINE & FRENCH LABORATORIES
leaders in psychopharmacological research

For prescriptions are only dispensable for re-sale in original packing, bearing our Special Label Beware of Imitations.

ADDORIN As a sedative	LEVYTORIN A sedative for	ALPHADOL A sedative for	BARBITAL A sedative for
AMBYGONIN A sedative for	SOORPHEN A sedative for	ISOPRAL A sedative for	RALGONINE A sedative for
ARISTOL A sedative for	NEOSONAL A sedative for	LYCTOL A sedative for	ROMATOR P.A.T.A.
AMPHIN A sedative for	WELWITOL A sedative for	NEOSTAN A sedative for	TAMIDIN A sedative for
CITANIN A sedative for	NURIN HYAL A sedative for	MILK ROMOTON A sedative for	TENON-SEE ASPI A sedative for
EPIDORIN A sedative for	ISODIVONIN A sedative for	PROTABDOL A sedative for	TRIDANAL A sedative for

VERONAL
THE NEW HYPNOTIC

Sedative Add in all qualities, Sedative of Sodium, Theobromine, Salol, Phenacetin, Salinal, Cromonal & Doxal - Bayer

G. ARNOLD, Sole Agent, 191 Clarence St., Sydney.

Valium
(Diazepam)
10

Roche

LADY JANE! PAINT IT BLACK! LONG LONG WALK!

mother's little helper

THE ROLLING STONES

A reminder advertisement - For prescribing information, please see B.L.S. or available literature.

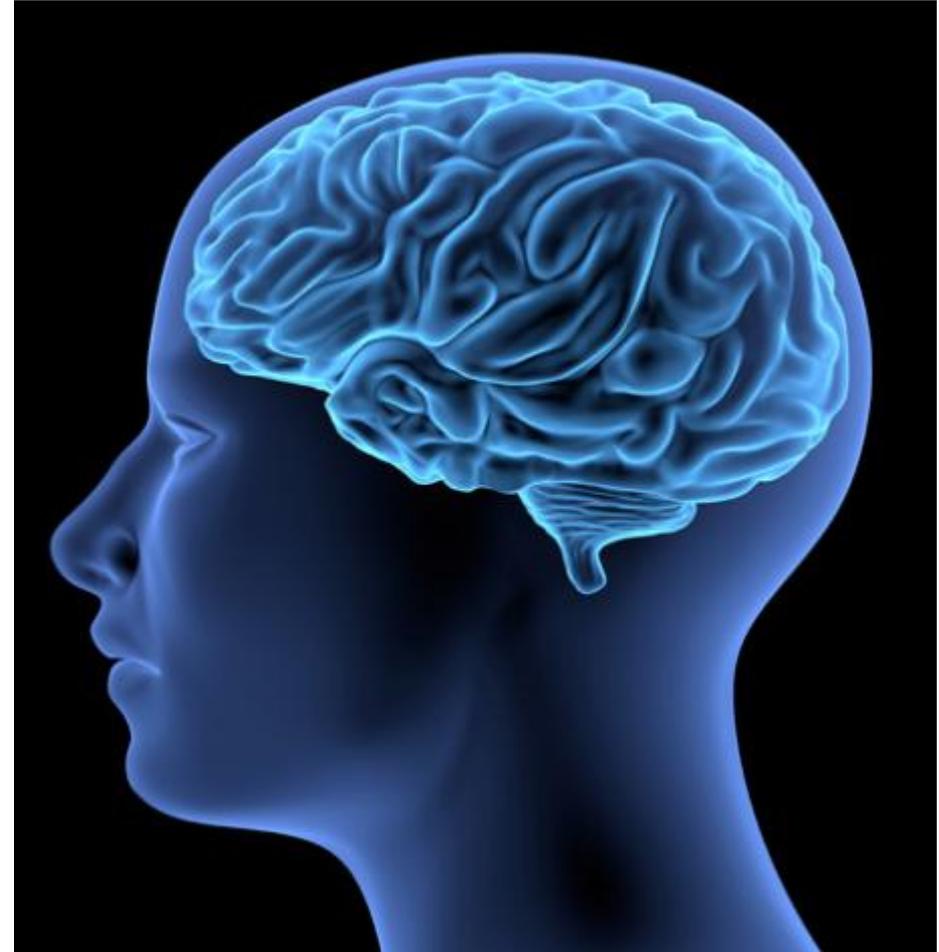
Roche Neuroscience focuses on three disease areas



Psychiatric disorders, including schizophrenia and treatment-resistant depression. Focus on treating negative symptoms and cognition.

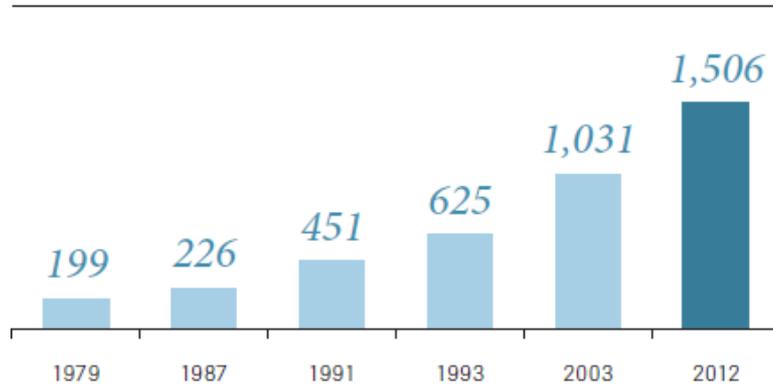
Neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease and Multiple Sclerosis. Focus on an early intervention and selection of patients eligible for a specific treatment based on biomarkers.

Neurodevelopmental disorders, including autism spectrum disorders, Down syndrome and Fragile X. Focus on the treatment of core symptoms, like social interaction, communication deficits and restricted repetitive behaviors.



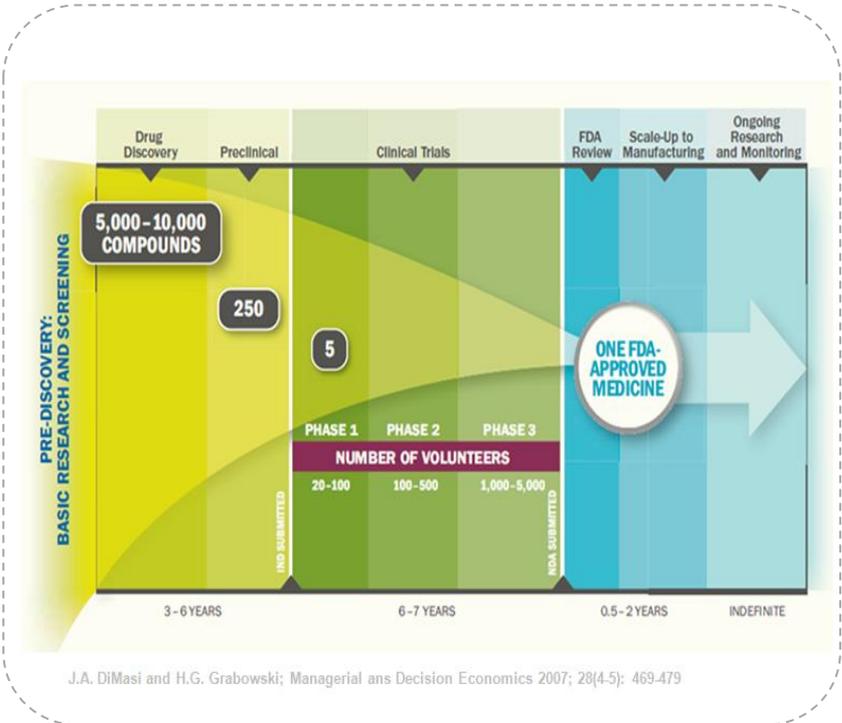
Unsustainable R&D Costs

Estimated cost of bringing a new chemical or biological entity to market in USD million¹¹



Source: J. Mestre-Ferrandiz, J. Sussex and A. Towse. The R&D cost of a new medicine. Office of Health Economics, December 2012 (Hansen, 1979; Wiggins, 1987; DiMasi et al, 1991; OTA, 1993; DiMasi et al. 2003; Mestre-Ferrandiz et al, 2012).

Long start up and conduction timelines



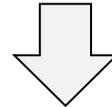
Drug Life Cycle « Current Trend »

- Long start up and conduction timelines
- Increasing complexity
- Low development success rate
- Unsustainable R&D costs
- New regulatory/reimbursement requirements

quotidianosanita.it

Demenze. Aifa: “Costi ricerca e tassi d’insuccesso elevati. Rischio disinvestimenti delle aziende. Serve coalizione globale”

- High cost of research and development of new molecules in neurology
- Delayed development of new drugs
- Low development success rate (number of inconclusive and/or negative studies)

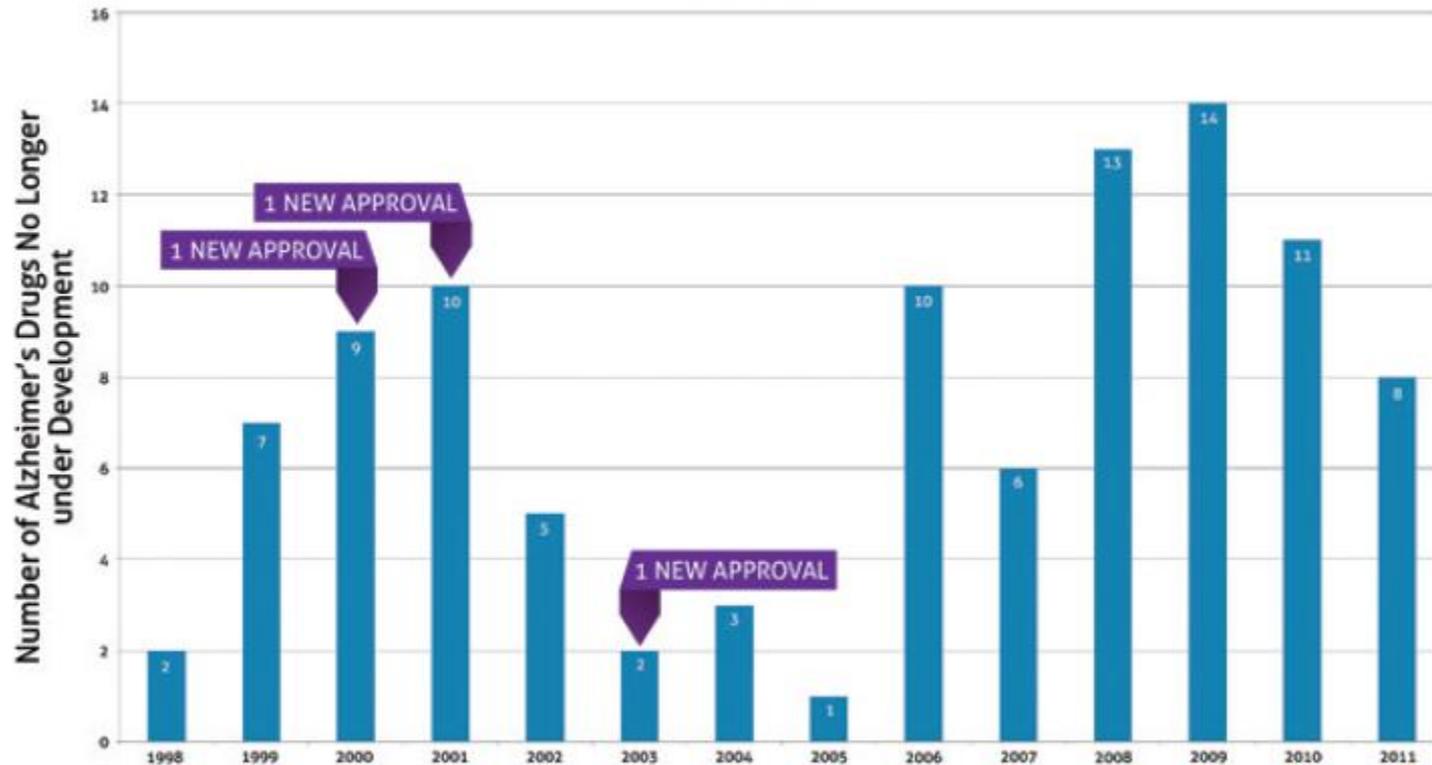


CNS is perceived as high level risk area

Low development success rate



Unsuccessful Alzheimer's Drugs in Development 1998 - 2011



Total unsuccessful drugs 1998-2011 = 101

2002- 2012: from 244 new drug in clinical development for Alzheimer's disease to 1 approval drug by FDA
Cleveland Clinic 2014

The most of current failure in phase II



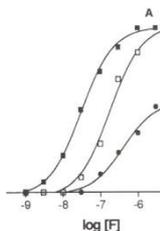
Failure and delays resulting
from suboptimal choices in four key areas



Initial test subjects



Dosing and administration



**Sensitive and early detection of
therapeutic effect**



**Recognition of differences between animal models
and human disease**



The Context



Key challenges and complexity



New frontiers



Conclusion

Key challenges and complexity



- Recruitment hurdles
- Clinical endpoints and biomarkers
- Placebo effect

PATIENT POPULATION

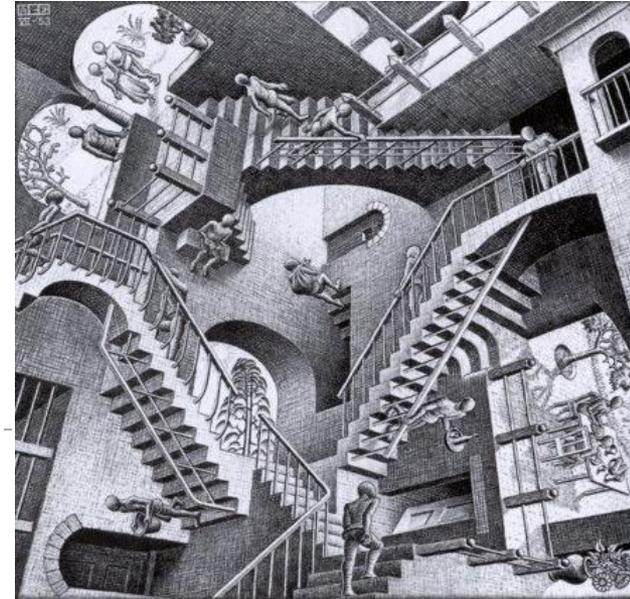
- Patient Flow
- Rarity of Patients
- Physical Immobility
- Co-morbidities
- Concomitant treatments
- Ability to provide consent
- Compliance to study drug

SOCIAL CONTEXT

- Involve Caregiver
- Few disease awareness
- Social Stigmatization

STUDY

- Complexity of Study Design
- Screening Procedures

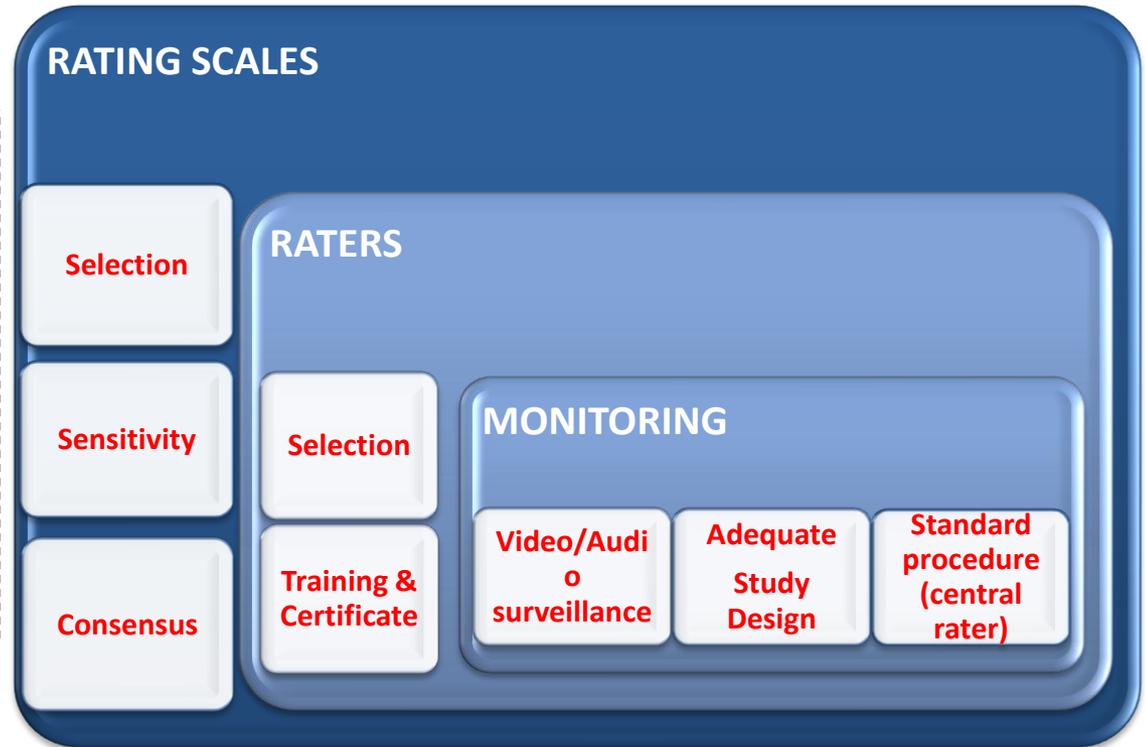


Key challenges and complexity



- Target population and management
- Clinical endpoints and biomarkers
- Placebo effect

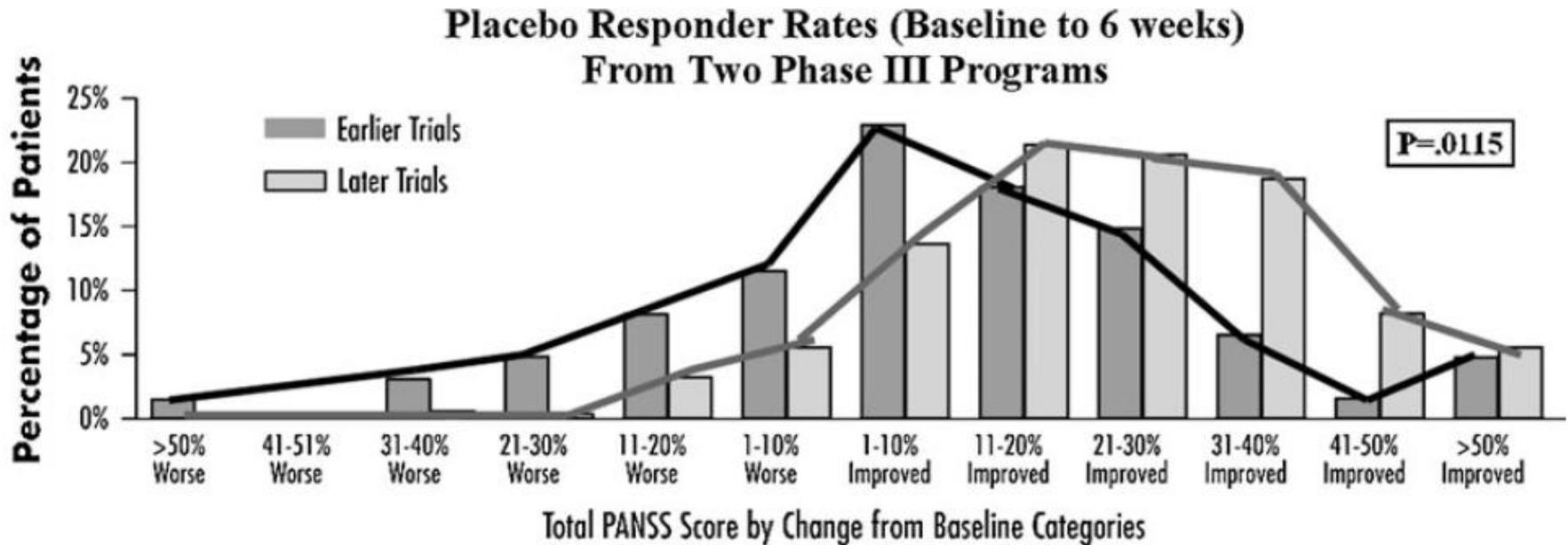
- It is expected to demonstrate efficacy on both a cognitive and a functional or global assessment scale
- Diagnose the disease in its early stages through the use of biomarkers to allow an early therapeutic intervention



Key challenges and complexity



- Target population and management
- Clinical endpoints and biomarkers
- Placebo effect





The Context



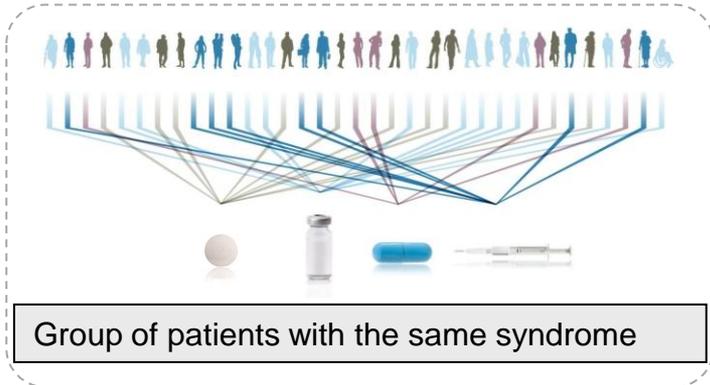
Key challenges and complexity



New frontiers

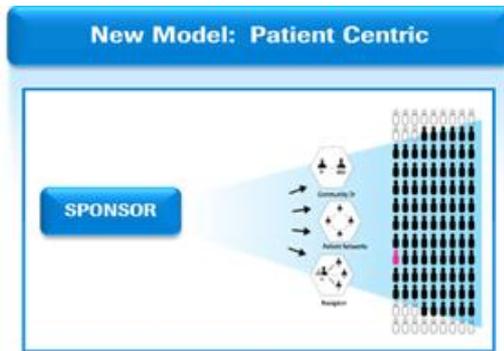


Conclusion



Personalized Healthcare

- To better understand disease diversity
- To identify the differences between patients
- To identify the best drug targets



Patient Centric Model

Easily and quickly reach targeted patients for clinical trials

New Technologies

- Biosensors/devices to objectively measure data traditionally self reported
- Provide an early intervention/coaching to enhance patient compliance and safety oversight



Decentralized Trials

- Increase trial participation/retention / compliance
- Ex. Mobile nurse, remote monitoring

- Adaptive design trials offer flexibility and the potential to identify failures earlier and increase efficiencies by focusing resources on therapies that have a greater chance of success
- Adaptive-licensing approach is based on a prospectively-planned process

ADAPTIVE DESIGN

Benefits to patients

- reduce the number of patients exposed to non-efficacious doses of the experimental drug
- early stopping so treatment practice can be changed rapidly

Benefits to the scientific quality of the study

- learn during the conduct of the study by improving the quality of decisions e.g. doses or schedules
- increased statistical power and precision of effect estimation

Benefits to Project overall

- improve project management and efficiency
- enhance efficiency and potentially decrease the duration of drug development

ADAPTIVE LICENSING

Maximise the positive impact of new medicines on public health by balancing the need for timely patient access with the importance of providing adequate, evolving information on a medicine's benefits and risks

Particularly relevant for medicines with the potential to treat serious conditions where there is an **unmet medical need**

European Medicines Agency launches adaptive licensing pilot project

[Press release](#)

19/03/2014

[European Medicines Agency launches adaptive licensing pilot project](#)

Improving timely access for patients to new medicines: pilot explores adaptive licensing approach with real medicines in development



The Context



Key challenges and complexity



New frontiers



Conclusion

Challenges and Opportunities

- High complexity
- Low development success rate

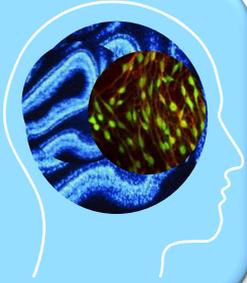


- Innovation
- Adaptive design and licensing

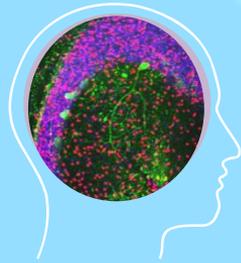
Why the investment in neurosciences?



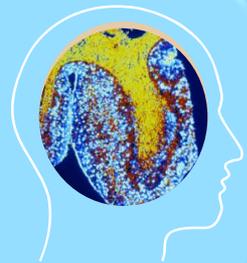
Psychiatric disorders



Neuro-degenerative disorders



Neuro-developmental disorders



Schizophrenia

26 million people

Alzheimer's Disease

18 million people

Autism

1% of the world population

Depression

350 million people

Parkinson's Disease

7-10 million people

Fragile X

rare

Multiple Sclerosis

2.3 million people

Down Syndrome

6 million people

Diseases of the nervous system may affect people in any stage of their lives and can substantially interfere with individual's ability to live an independent and fulfilling life. This may cause a significant strain not just on the patient but also on families, caregivers and society.

We can build a better future with medicines that make a real difference to patients.

Doing now what patients need next



«Don't be satisfied with the horizon, keep looking for infinity » Jim Morrison