Technology and the Future of Cognition

Regulatory Considerations in Clinical Studies on Cognition

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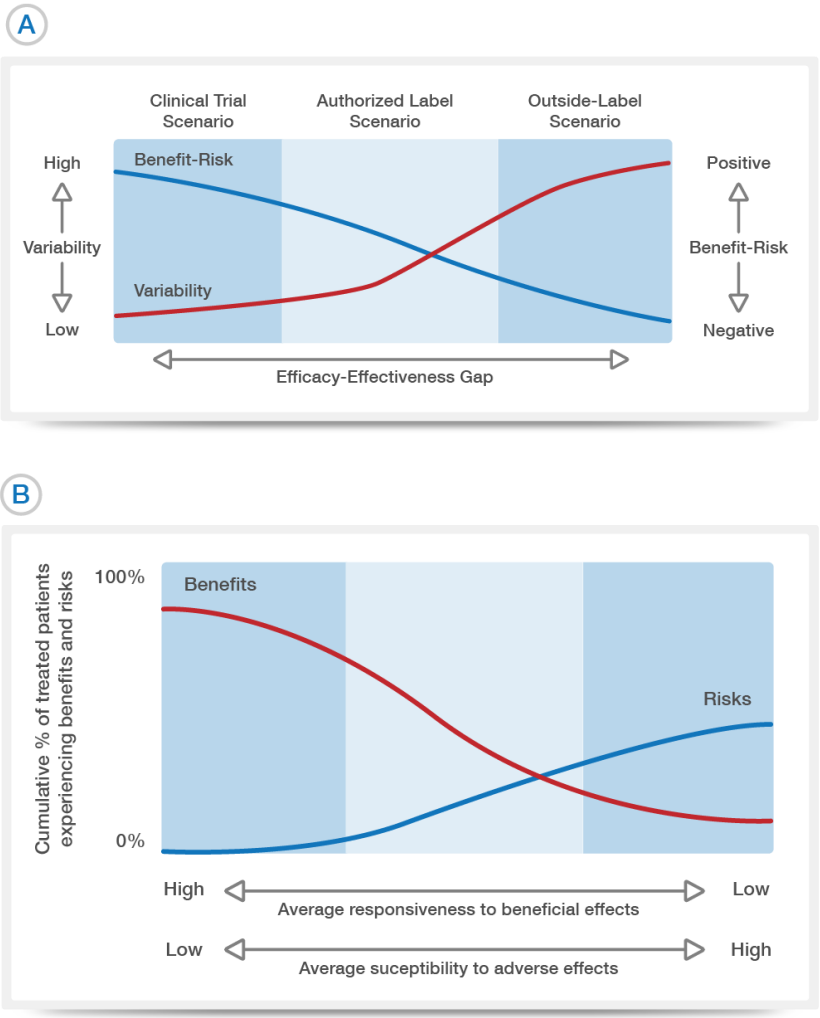
Efficacy - Effectiveness Gap & Patient Heterogeneity: One Size Doesn't Fit All

Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response.

Hans-Georg Eichler, Eric Abatme, Alasdair Breckenridge, Bruno Flamion, Lars L. Gustafsson, Hubert Leufkens, Malcolm Rowland, Christian k. Schneider and Brigitte Bloechi-Daum

Big challenge for the regulators:

- Adequate predictive value of the biomarker test (false-negative & false positive patients)
- How big a difference between the subpopulations identified by a companion diagnostic or an ecological measurement could justify a label claim?



Emerging Regulatory Trends For New CNS Therapies

Better understanding of patient subgroups of complex diseases which could result in a better design and outcome of late-stage development

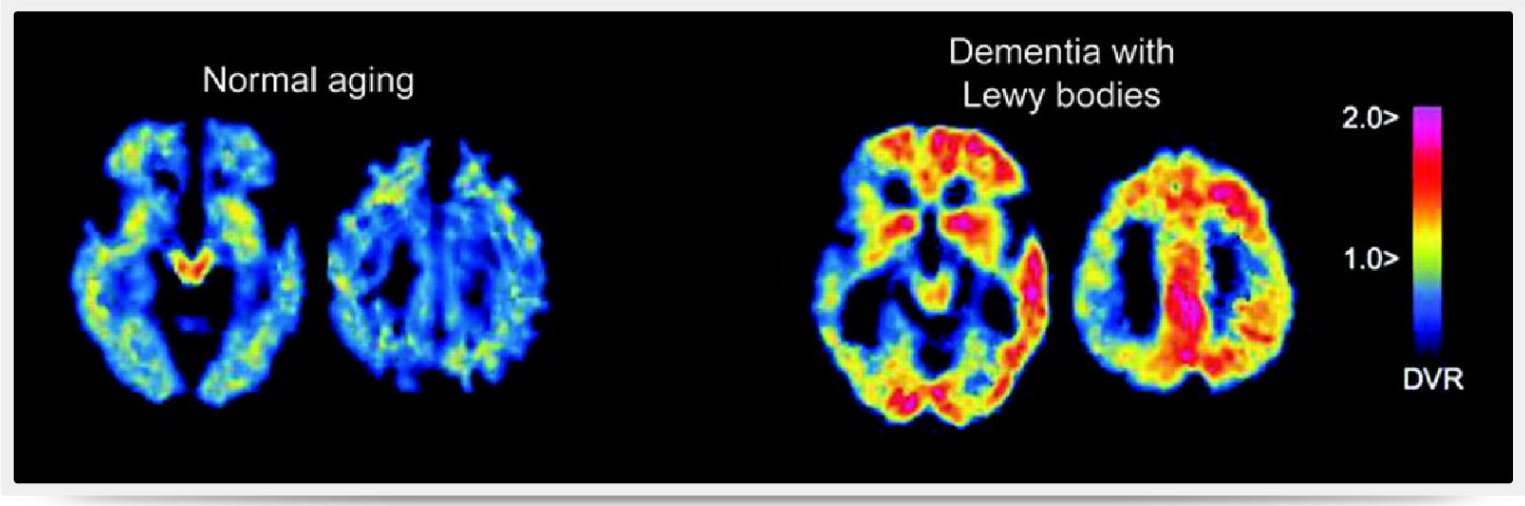
Regulatory openness to discuss potential new target populations or indications

Tailoring For Subpopulation In Dementia

Treatment of individuals with drugs targeting the amyloid system may require a “hyper-amyloid patient” in order provide proof of concept, effective response and disease-modifying abilities.

- The status of the amyloid may change during the course of the disease.
- Further understanding the underlying mechanism of amyloid deposits and dysfunction in (pre)-dementia may lead to additional pharmacological strategies to treat the disorder.

Amyloid Burden (PIB)



Some of the Current Studies In Well-Defined Sub-Populations

- Dominantly Inherited Alzheimer Network (DIAN)
- Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation.
- Genetics of Mendelian Forms of Young Onset Alzheimer Disease (GMAJ)
- A Study of Crenezumab Versus Placebo in Preclinical PSEN1 E280A Mutation Carriers to Evaluate Efficacy and Safety in the Treatment of Autosomal-Dominant Alzheimer Disease, Including a Placebo-Treated Noncarrier Cohort.
- More for ApoE4 omozygotes…

Regulatory Consideration

Extrapolation and modeling for:

- Population (Diagnosis)
- Trial (Design)
- Outcome (Endpoints or biomarkers?)

Extrapolation and Modeling: Population

Extrapolation and modeling to:

- What are the differences and similarities between familiar and sporadic AD?
- Is the clinical picture similar?
- What is the lag of time between appearance of neuropathology and onset of symptoms in familiar AD?
- Which factors influence the duration of the symptom-free period?
- How is AD diagnosed in ApoE4 Carriers?
- Which is the best diagnostic biomarker in familiar AD?
- Are results replicated in ApoE4 carriers?

Extrapolation and Modeling: Trial Design

- Does the course of the disease differ between familiar and sporadic AD?
- Is the speed of progression similar?
- Which factors influence the course and progression of the disease in well-characterized populations?
- Could these factors be controlled in a clinical trial?
- Could a multidomain platform such as the one from the FINGER trial (diet, exercise, vascular risk monitoring, cognitive training) be included in a trial?
- Does cognition predicts function in well-characterized populations?

Extrapolation and Modeling: Outcome

- Could results in cognition be extrapolated to predict results in the functional domain?
- Should we use clinical endpoint in pre-clinical stages?
- Should we instead use biomarkers only?
- What is the predictive value of biomarkers as outcomes in well-characterized populations?

Endpoints for Relative Effectiveness Assessment (REA)

International Journal of Technology Assessment in Health Care, 30:5 (2014), 508–513.

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ENDPOINTS FOR RELATIVE EFFECTIVENESS ASSESSMENT (REA) OF PHARMACEUTICALS

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Definitions

A **clinical endpoint** describes a valid measure of clinical benefit due to treatment: it is a direct measure of how a patient feels, functions and survives (3,4)

A **surrogate endpoint** is an endpoint that is intended to replace a clinical endpoint of interest that cannot be observed in a trial, expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. An improvement in surrogate endpoint may be or may not be perceived by the patient. In many cases, surrogate endpoints do not themselves directly measure a clinical benefit (3,8,9,10,11).

A **biomarker** is a characteristic that is objectively (reliably and accurately) measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention (e.g. HIV viral load). The biomarker must lie on the pathophysiologic causal pathway of the disease; it must be correlated with a clinical endpoint to be useful in detecting disease and assessing prognosis, and validated through a validation or qualification process. A biomarker may be used as a surrogate endpoint when it substitutes for a clinical endpoint (3,8,9,10,11).

An **intermediate clinical endpoint** is a clinical endpoint such as measure of a function or of a symptom (e.g. angina frequency), but is not the ultimate endpoint of the disease, such as survival or the rate of irreversible morbid events (stroke, myocardial infarction); improvement in an intermediate endpoint due to treatment can be of value to the patient even if it does not lead to the improvement of a final endpoint (4).

A **composite endpoint** combines two or more of single events (in one endpoint showing the overall and clinically relevant treatment effect (12).

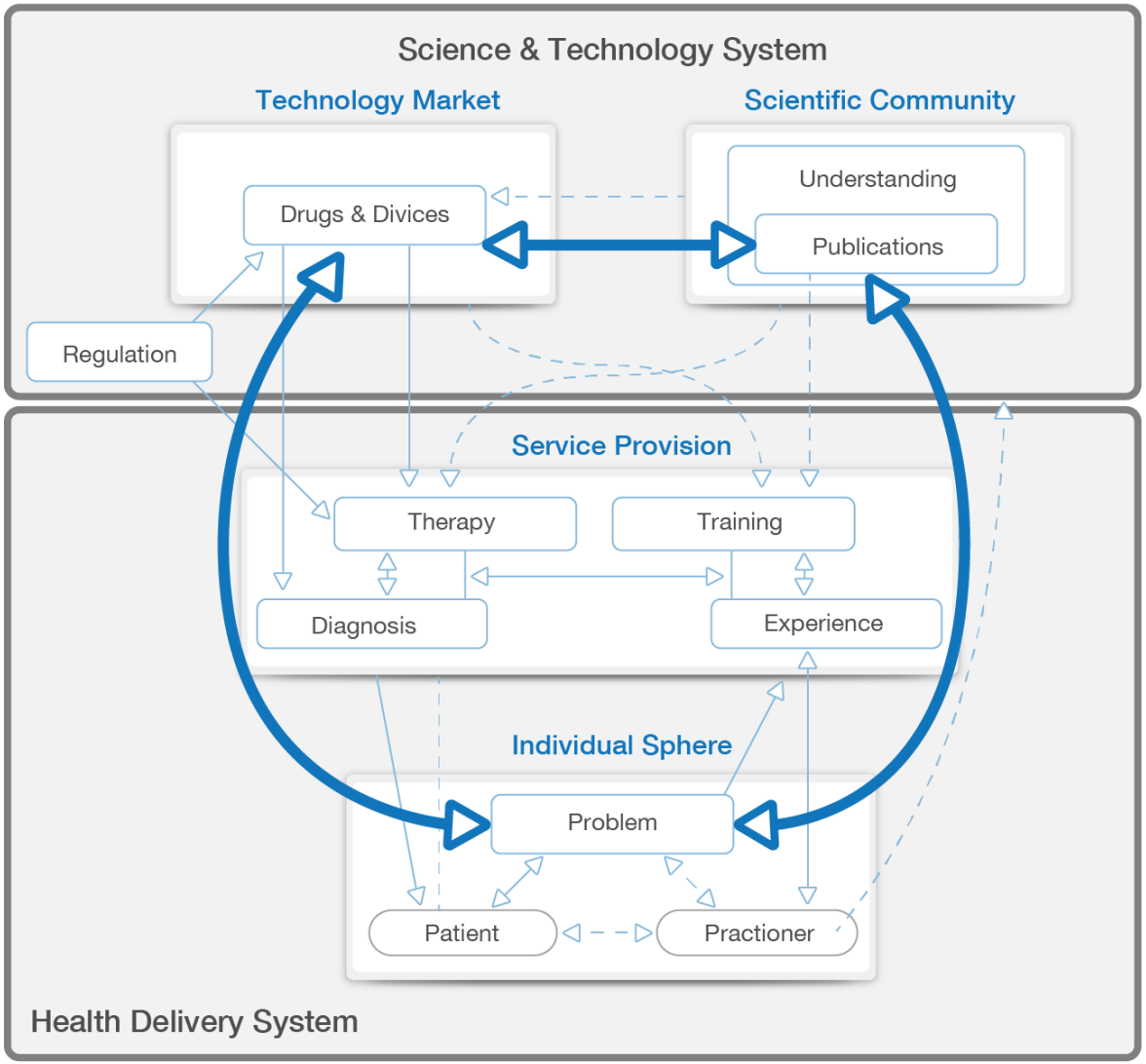
Patient reported outcomes (PRO) is an umbrella term used to describe any outcome evaluated directly by the patient himself/herself, without interpretation by clinicians or others, and based on patients' perception of a disease and its intervention(s) (5,6).

Health-related quality of life (HRQoL) is a broad concept which can be defined as a patient's general subjective perception of the effect of illness and intervention on physical, psychological and social aspects of daily life. HRQoL represents a specific type/subset of patient-reported outcomes (PROs), distinguished by its multi-dimensionality (5,6,7).

Utility measures for HRQoL are measures that lead to a single score for HRQoL with specific properties (score on 0 (=death) to 1 (=perfect health) scale). In contrast to the summary item scores or aggregate HRQoL scores obtained by summing weighted or unweighted item or dimension scores, utilities are obtained using preference-based or choice-based methods. Utilities could reflect either patients' preferences for specific health states or the general public's preferences for these states (7).

Endpoint Category	Examples
Mortality	• Overall survival
Morbidity	• Cardiovascular mortality • Clinical events: myocardial infarction, stroke, asthma exacerbation, • Symptoms: pain, dyspnea, anxiety • Function: activities of daily living, exercise tolerance • Adverse events: serious adverse events,withdrawal from treatment due to adverse events, disease and treatment-related adverse events (e.g. hypoglycemia in diabetes; bleeding in anti-coagulation, fatigue in chemotherapy)
Health Related Quality of Life	• Generic questionnaires: Short-form(SF)-36; Sickness Impact Profile, • Disease-specific questionnaires: Asthma Quality of Life Questionnaire, Dermatology Life Quality Index, • Generic utility instruments: EuroQol-5dimension, Health Utilities Index & Quality of Well-Being

Remember the Health Technology Assessment of Innovation



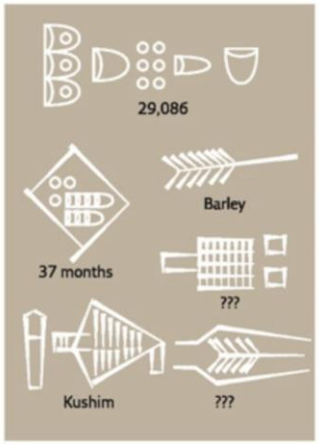
A common definition of what constitutes an 'innovative medicine' is currently lacking.

From a public health perspective, the level of innovativeness of a medicine is primarily defined by the benefits the medicine generates for patients.

These can be in the therapeutic, clinical or quality of life domains, but also in the socioeconomic domain.

General Conclusive Remarks

- Apply translational science to regulatory validated concepts/measures
- Follow guidelines not gimmicks, gadgets or gurus to certify valid measures
- Consider that Homo Sapiens has not used symbols for 95% of its history
- Evolutionary cognition could help in addressing some of the modern issues



Kushim is the first recorded name in history.
Is an accountant who signed a tablet reading:
“29,086 barley units received in 37 months”
In Uruk, 3,400 BC