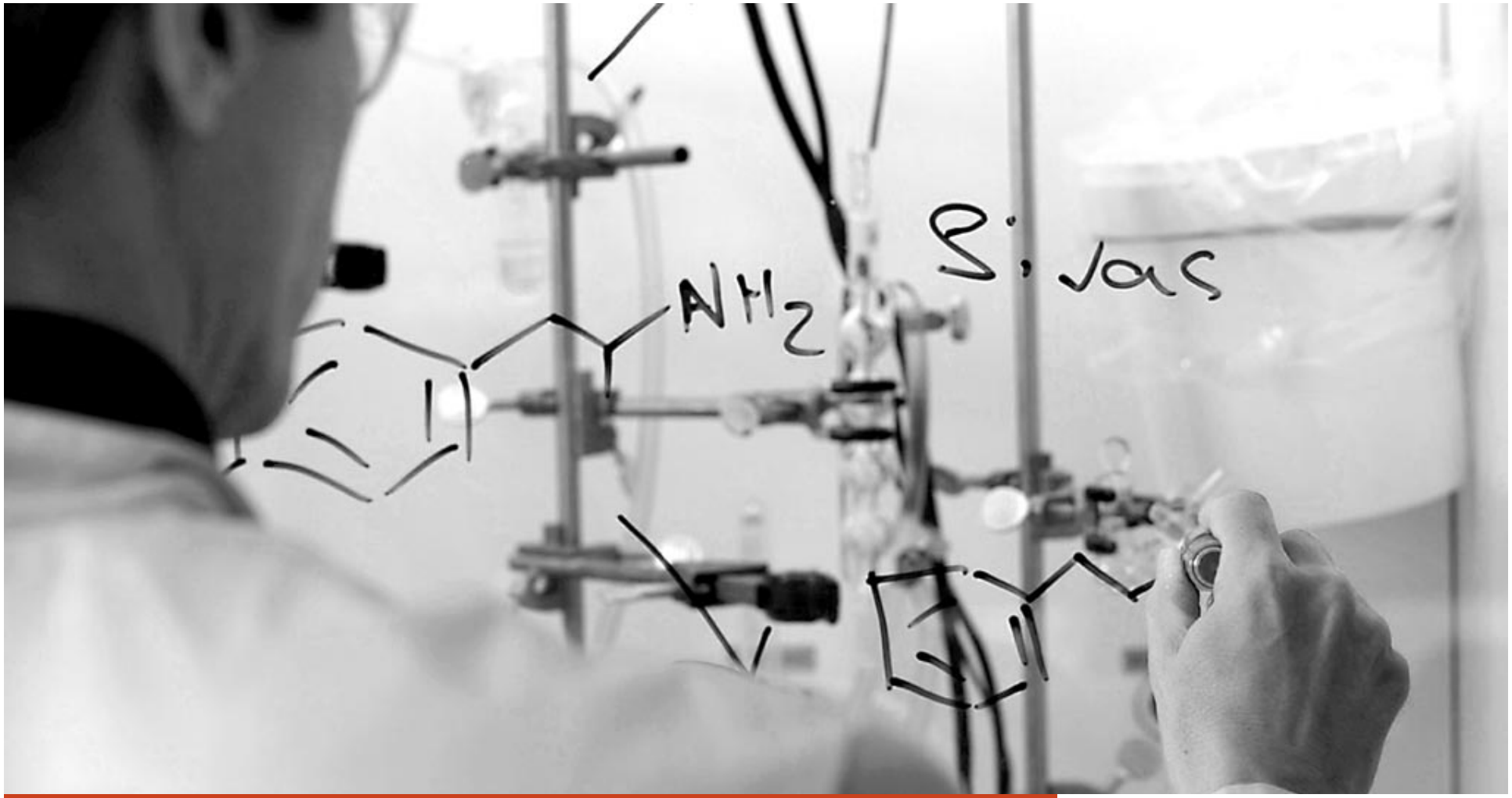

COMPLEX STUDIES – TURNING SCIENTIFIC IDEAS INTO REALITY

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Lundbeck PROGRESS IN MIND

For complex (non-standard) phase I studies, new designs and types of measurements are often introduced and challenges are seen in getting internal alignment in the study team – in particular around the data collection, reporting and output of those non-standard data.

This session will focus on how the scientific complex ideas are “transformed” into an actual study protocol and produce useful data as a result.

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The CNS Landscape

- Large unmet need for new and innovative treatments within brain diseases
- The underlying biology is poorly understood
- Subjective diagnosis rather than objective biological measurements

- A clear link between biology, diagnosis and drug effects are needed

MONTGOMERY AND ASBERG DEPRESSION RATING SCALE

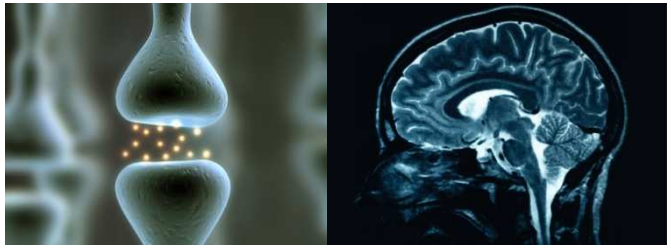
1 - APPARENT SADNESS - *Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.*

0 No sadness
1
2 Looks dispirited but does brighten up without difficulty
3
4 Appears sad and unhappy most of the time
5
6 Looks miserable all the time. Extremely despondent.

☐

Br. J. Psychiat. (1979), 134, 382-389
©Stuart Montgomery 1978, Measures of Depression, Fulcrum Press, London

Lundbeck's Strategy



- Lundbeck has specialised in brain diseases
  - Depression and anxiety, psychotic disorders, epilepsy and Huntington's, Alzheimer's and Parkinson's diseases and alcohol dependence

- Lundbeck's R&D strategy:
  - develop drugs that target the underlying mechanisms of brain diseases in order to treat the symptoms more effectively
  - potentially alter the course of the diseases
- The strategy requires:
  - comprehensive research into the brain and the biology and mechanisms of brain diseases
  - improved understanding of research targets and clinical outcomes

→ development new biomarkers

→ describe the pharmacology of drugs with new targets

→ via complex and exploratory studies

The streetlight effect

A policeman sees a drunk man searching for something under a streetlight and asks what the drunk has lost. He says he lost his keys and they both look under the streetlight together.

After a few minutes the policeman asks if he is sure he lost them here, and the drunk replies, no, that he lost them in the park. The policeman asks why he is searching here, and the drunk replies, "this is where the light is".

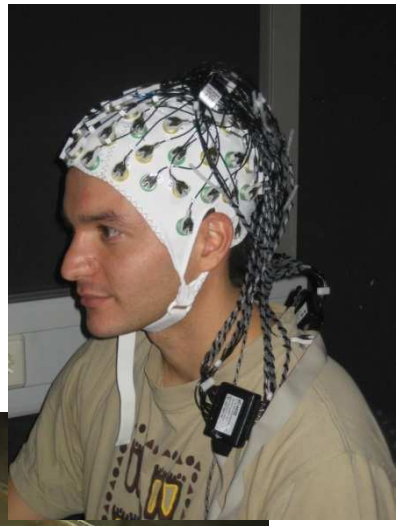
What is meant by ‘new methods’?

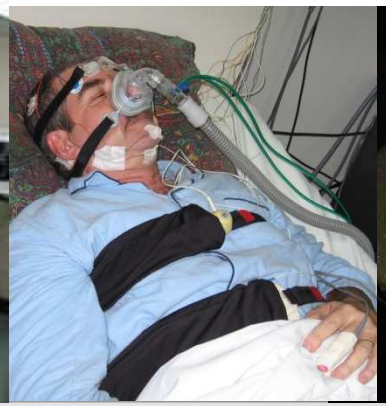
- New to the sponsor
  - Used in no or a few studies before
  - Limited knowledge internally
  - Not integrated in standards and tools (protocol, CRF, data formats etc.)
  - Can be well-stablished and validated by others

- Exploratory, non-validated methods
  - Not well-established or validated
  - No party (sponsor, clinical site, experts) has the full overview of how to ‘operationalise’ the method

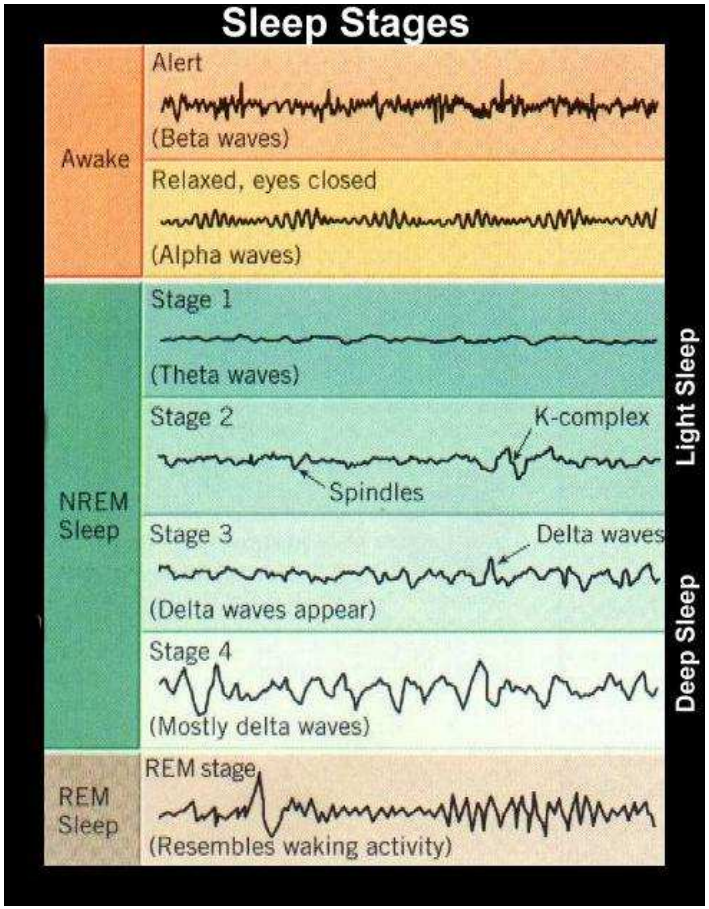
Examples of Complex Studies

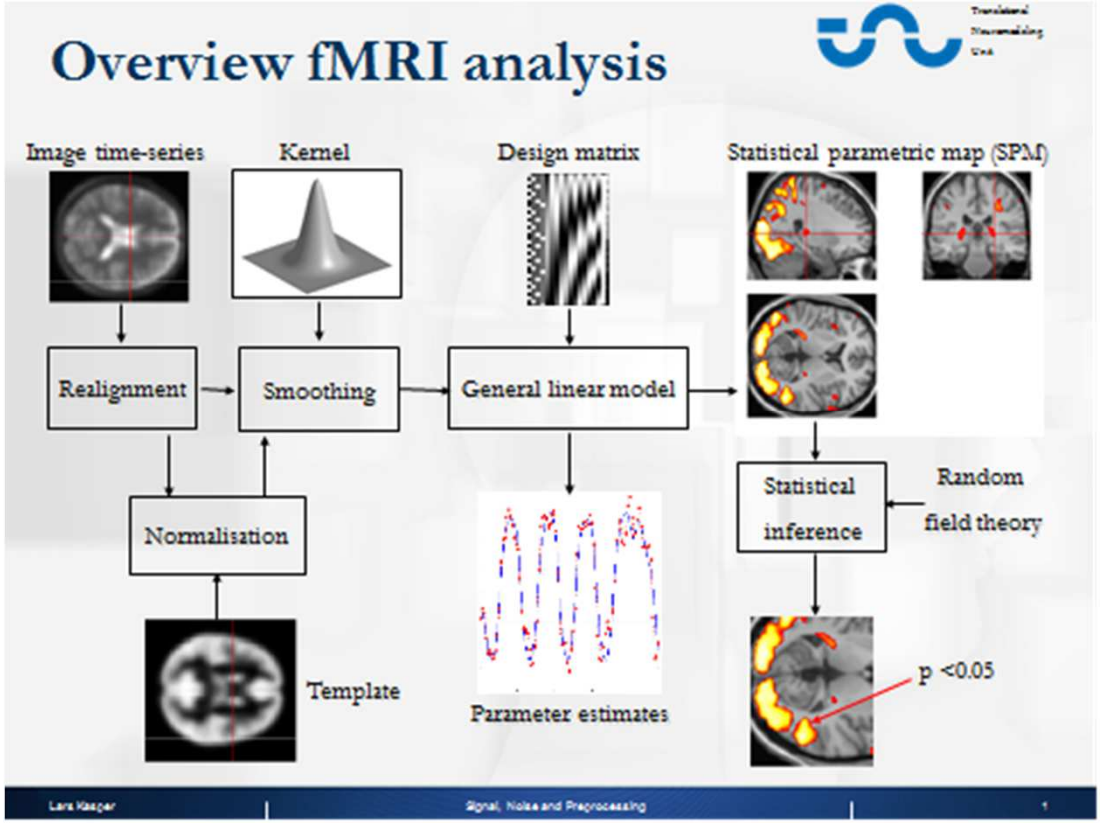
- Behavioural tasks, fMRI scans and alcohol infusion (patients with alcohol dependence)
- Cognitive tests and fMRI scans (subjects remitted from depression)
- Cognitive tests and EEG (healthy subjects)
- Sleep EEGs (polysomnigraphy) (healthy subjects)
- UV-B irradiation, 4 pain models, skin biopsy (healthy subjects)
- PET studies (healthy subjects, patients with schizophrenia)
- PET ligand development (healthy subjects)





Example of Complex Data Analyses





Challenges of New Methods

- How to transform the scientific ideas into a usable data output?
- How to get the overview/understanding of the relevant steps in the process
- No one team member or party (sponsor, clinical site, experts) have the full overview of the data ‘life-cycle’
- The experts on the method are often external – how to integrating their knowledge into the study team?
- Deliver complex studies with new assessments fast and to a good quality/in a usable format
- Complex outsourcing – many parties involved – how to get them on board early enough?

What can go wrong? A few examples

- Unclear guidance on how to capture data in the CRF
- Data formats not defined in detail (e.g. no. of decimals)
- Time windows defined too narrow resulting in too many data queries
- Data not delivered in the expected format due to lack of detailed data transfer specifications

– and the consequences

- Expensive and time consuming updates to the eCRF
- Substantial delays in database release

What needs to be defined for a new method?

Will Data unblind study?

Data Capture – Source data and CRF design

END POINTS

Archiving of data

How to perform the assessment

Objectives

Data Querying – How to monitor and query the CRF?

Data Format (CDISC)

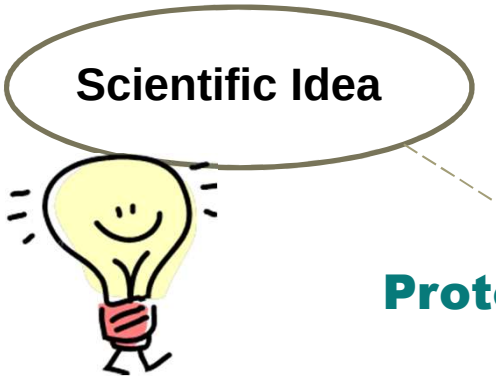
Data Transfers

How to report the results

Overview of data flow

Equipment

Documents involved
- and how things are often defined



CRF completion guidance

Edit Check Specifications

CRF

Statistical Analysis Plan

Protocol

Data Transfer Specifications

Study Operations Manual

SDTM (CDISC) data format

Source Data Identification Form

TFLs

Work orders

Clinical Study Report

Specialist Report?

Describe the data life-cycle of each assessment

How to perform the assessment

Data Querying – How to monitor and query the CRF?

Data Capture – Source data and CRF design

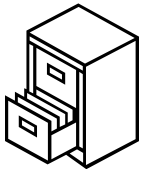
Will data unblind the study?

Data Transfers

Data Format (CDISC)

How to report the results

Archiving of data



Team Work

- No individual team member or party have the full overview of the data life-cycle
- Expert to expert communication is essential
- Preferably face-to-face meetings between sponsor, and all vendors

Sponsor

- Clinical pharmacology scientist
- Study manager
- Data manager
- Statistician
- Programmer
- Outsourcing manager

Vendors

- Investigator and clinical site
- Expert on the method
- Labs
- Biometric CRO

A Few Words on Vendor Management

- Important for work orders
  - Specify expectations in expert-to-expert communication between different vendors
  - Coordinate dates for data transfers and expert reports across vendors
  - Milestone payments dependent on delivery of data in the agreed format

- Meetings (TCs) with all vendors to coordinate data transfers
  - In the planning phase and if needed just before data transfers

Standards and tools – what have we done at Lundbeck?

- Comprehensive protocol template
  - A lot of guidance
  - Standard scenarios outlined
- The statistical analysis plan integrated in the protocol
  - Complete analysis and presentation of data defined at the time of protocol writing
- Standard tables, figures and listings
  - A set of standard TFLs
  - A matrix to guide which TFLs to use for which type of study
- Points to consider for new methods
  - An overview of what to define, in which documents and who is involved

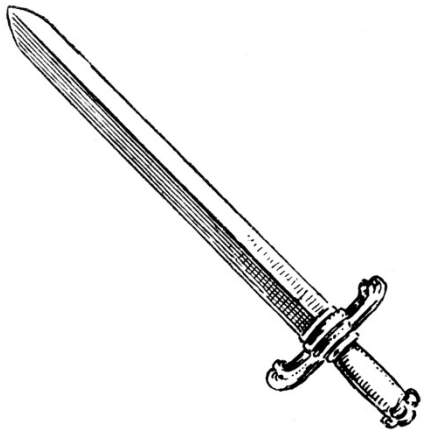
Points to consider for new methods

Questions	Details	Documents	Roles
Objective/purpose of the assessment	Exploratory/confirmatory? Psycometric scales: diagnosis, baseline characteristics, safety marker, PD/efficacy marker	Protocol	CPS, BS
Endpoints	Define endpoints Derivation of parameters	Protocol SAP	CPS,
Overview of sequence of assessment	Tests, familiarisation	Protocol Details in Study Operations Manual?	CPS,
How to perform the assessment	Conditions (sound, light, temperature) Tests, familiarisation by the subjects	Protocol Details in Study Operations Manual?	CPS, site, provider of equipment
Certification/training of the clinical staff performing the tests	Rater qualifications/certifications		CPS, ?
Equipment	Specify equipment Rental/shipment of equipment	Protocol Details in Study Operations Manual? Work order	CPS, CPSM, site, provider of equipment
Data Capture – How to fill in the CRF?	New CRF page, what to capture in the CRF and what to capture elsewhere? Define the data source Data format (decimals, …)	CRF Source Data Identification Form CRF completion guidance	CPS, CPSM, DM, BS
Data Querying – How to monitor and query the CRF?	Validation checks on the data (accepted range of values, positive/negative)	ECS CRF completion guidance	CPS, CPSM, DM, BS
Data blinding	Can the data unblind the study?		
Data Format	Raw and derived data? Define non-standard SDTM format	Annotated CRF	CPS, DM, BS
Data Transfers	Overview of data flows Frequency of transfers Data needed during or at end of study? Data transfers dates must be coordinated across vendors	Data Management Plan Data Transfer Specifications	DM, CPS

Well established standards – a two edged sword

Pros

- Off the shelf, easy to use methods are a prerequisite for efficiency
- Frees up resources to focus on the new methods



Cons

- You forget what it takes (knowledge, time) to develop and implement new methods
- You don’t understand the method in detail
- You forget that it took several years to make it an ‘off the shelf easy to use’ standard method

Conclusions

- Implementing a new method is a complex tasks
- No individual team member has the full overview of the process

- Key things needed to be successful:
  - A common understanding in the team of the life cycle of the data collected
  - Team collaboration to define all steps in the process
  - Meetings (preferably face-to-face) between all parties (internal and external): scientist, study manager, data manager, biostatistician, experts on the method