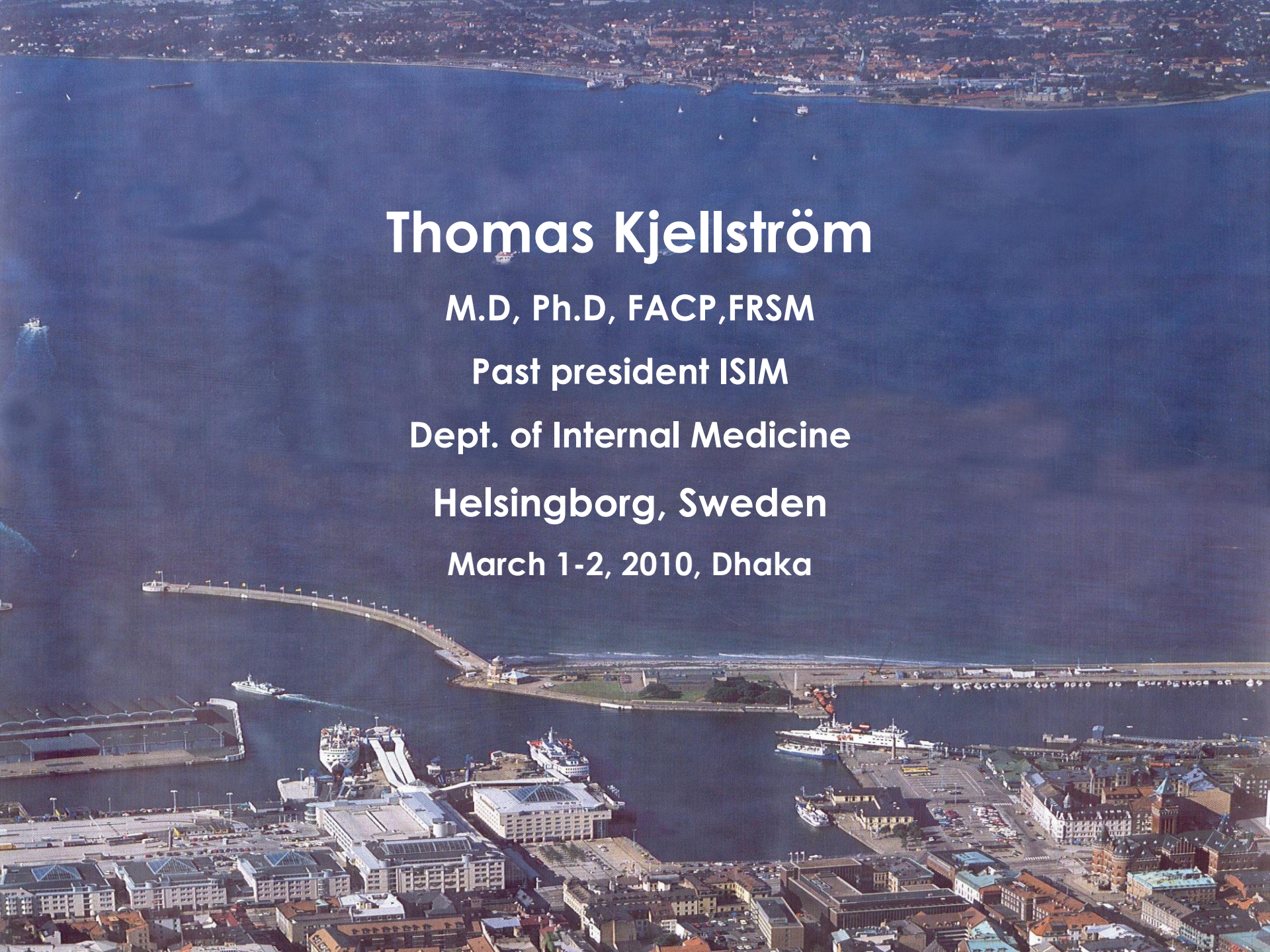


Thomas Kjellström

M.D, Ph.D, FACP,FRSM

Past president ISIM

Dept. of Internal Medicine

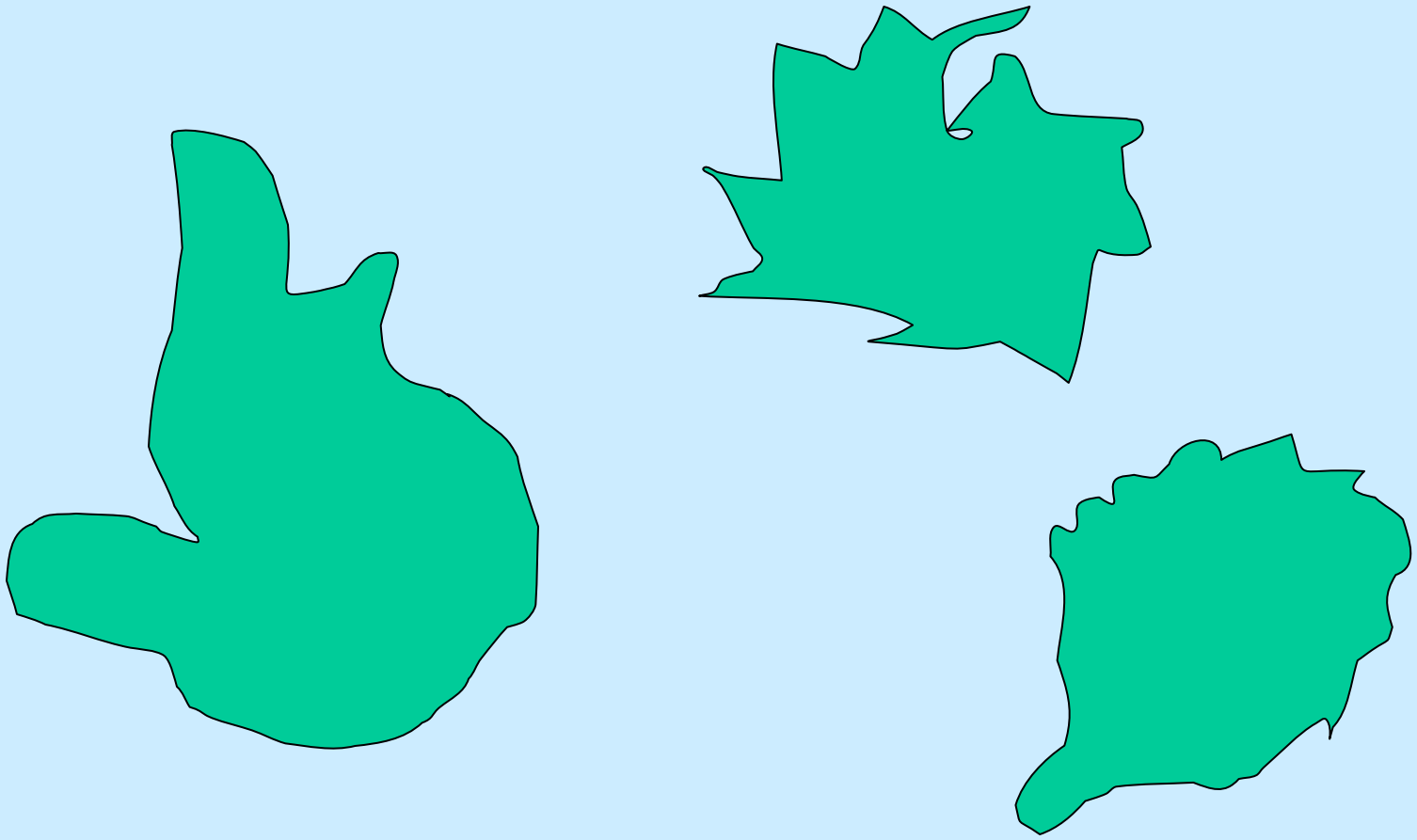
Helsingborg, Sweden

March 1-2, 2010, Dhaka

From Trials to Practice

Patient Selection for Treatment

Islands of knowledge



Clinical trial

1. Preclinical development
2. Trials on humans

   Phase 1. Volunteers

   Phase 2. Patients

   Phase 3. Studies on patients and controls
3. REGISTRATION

   Phase 4. Clinical experience

Planning of a clinical trial 1(2)

0. Idea - hypothesis
1. What is in the literature?
2. Formulating the problem
   a) Rational
   b) Hypothesis
   c) Aim
3 Synopsis – target population, sample size, budget
4. Searching for trialists
5. Protocol – draft
6. Economy
7. Written agreements
8. Ethical committee
9. Organisation of the study

Cont. **Planning of a clinical trial 2(2)**

10. Manual for the trial
11. Quality assurance
    - laboratory samples
    - end-point validation
    - total quality
12. Selection of trialists
13. Final protocol
14. Final trial manual
15. Computerized programs
    database
    tests of programmes
16. Education of trialists
17. Equipment for trial centres
18. Recruiting patients
19. End of the planning phase

THOSE who think

they know it all

are very annoying

to those of us

WHO DO

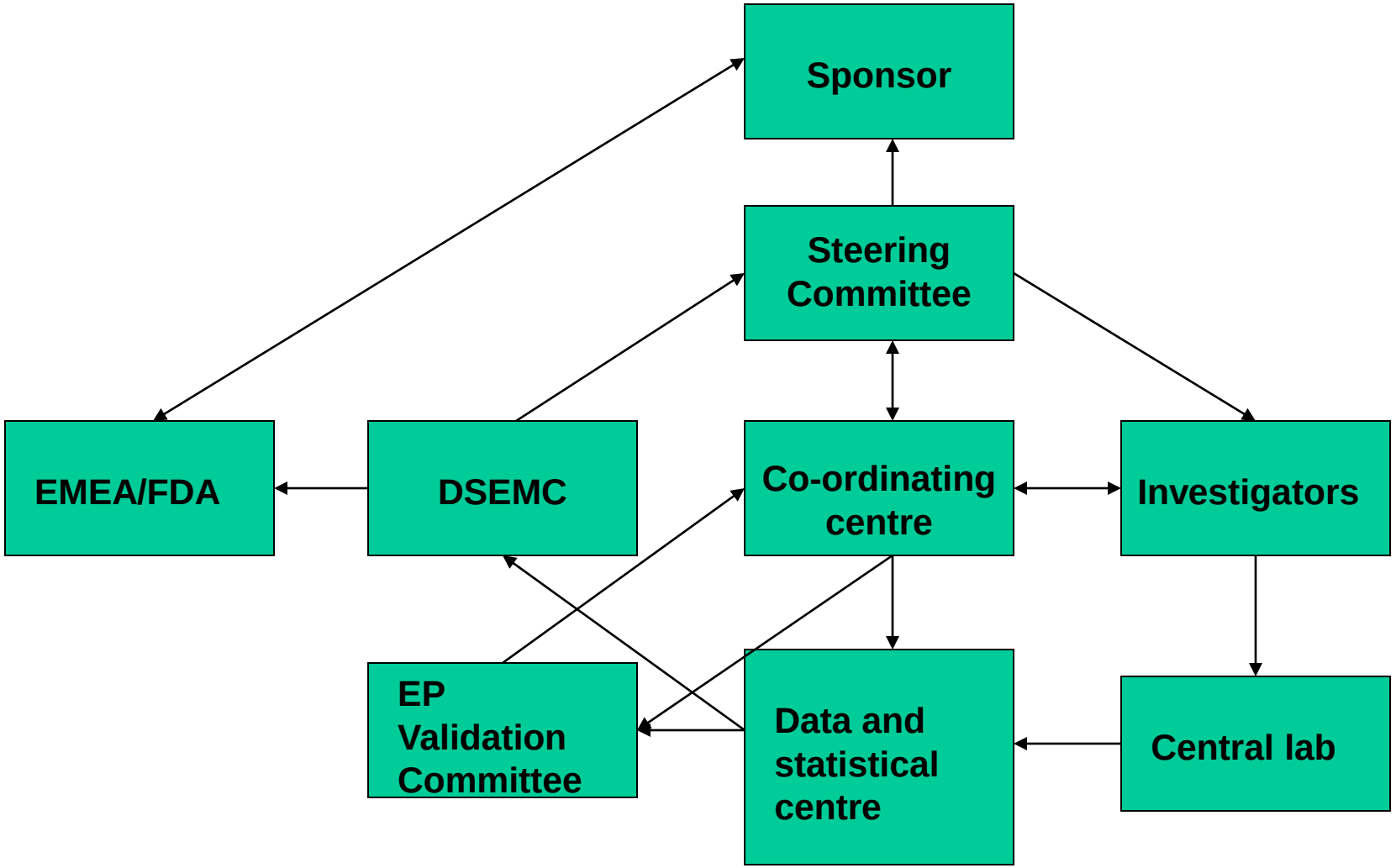


Fig 3 The organization of a trial. EMEA, European Medicin Evaluation Agency; FDA, Food and Drug Administration. For other acronyms see text

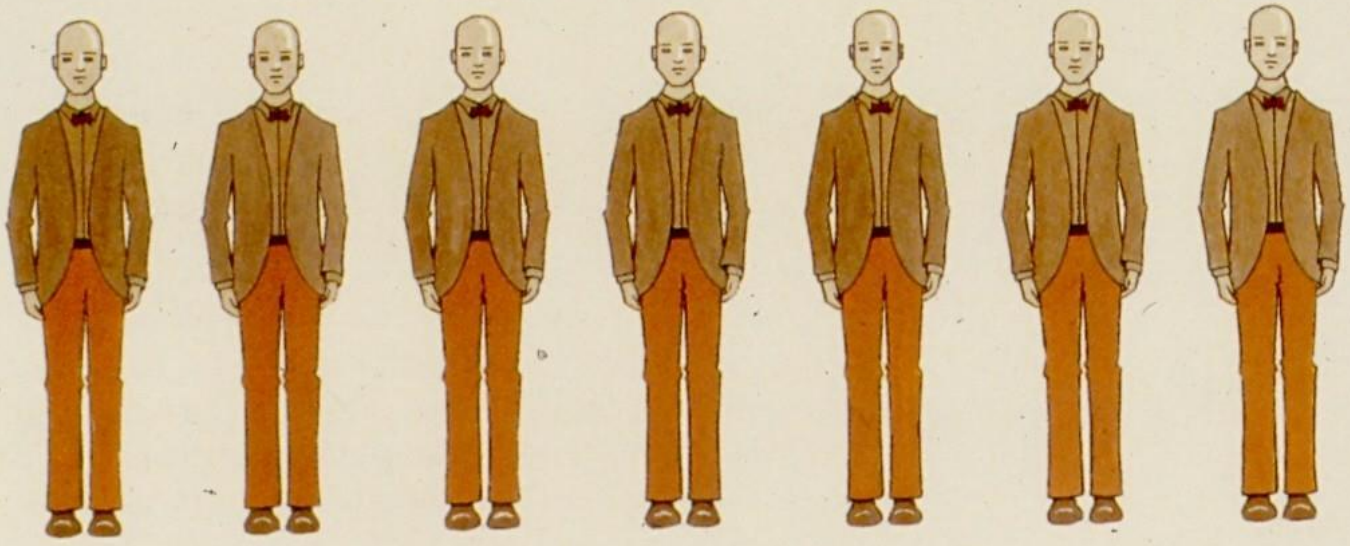
QUALITY OF A TRIAL

a) Relevance in the design

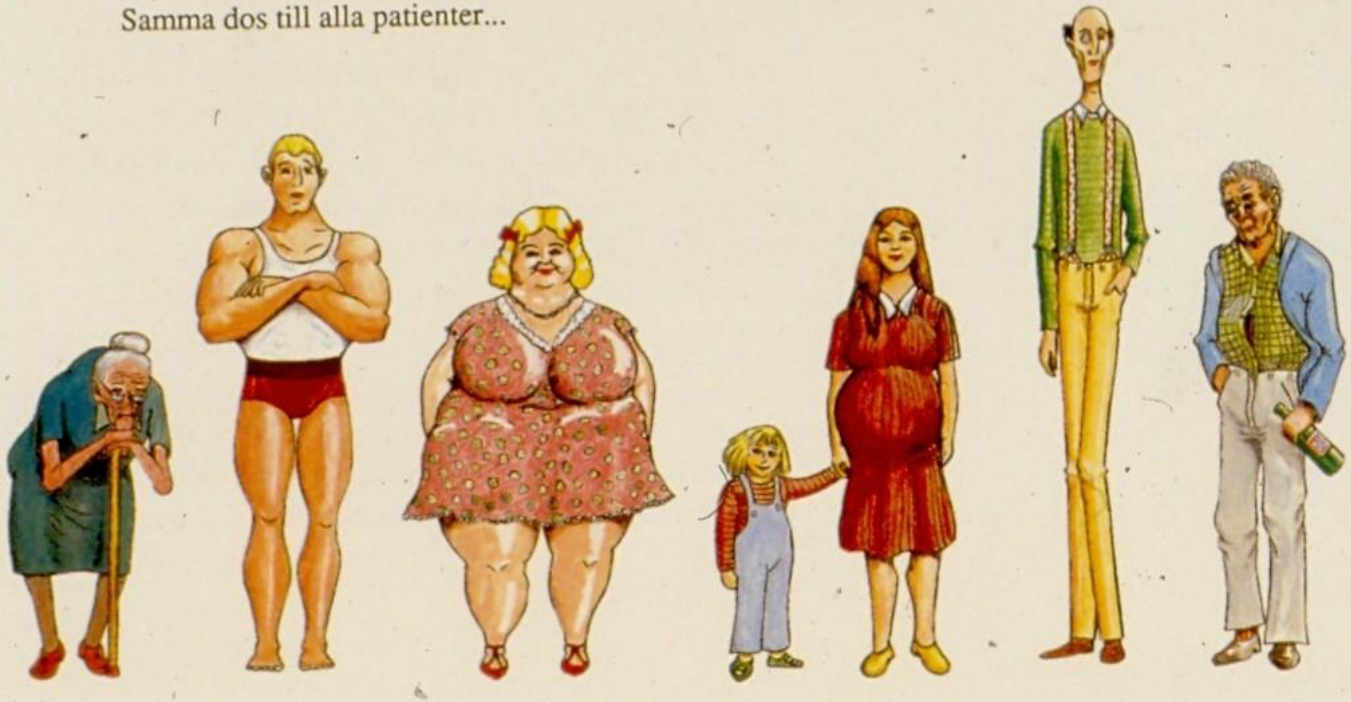
b) Quality of the protocol

c) Quality in performance

d) Quality in the database !!!!
(depending on the quality in the planning phase)

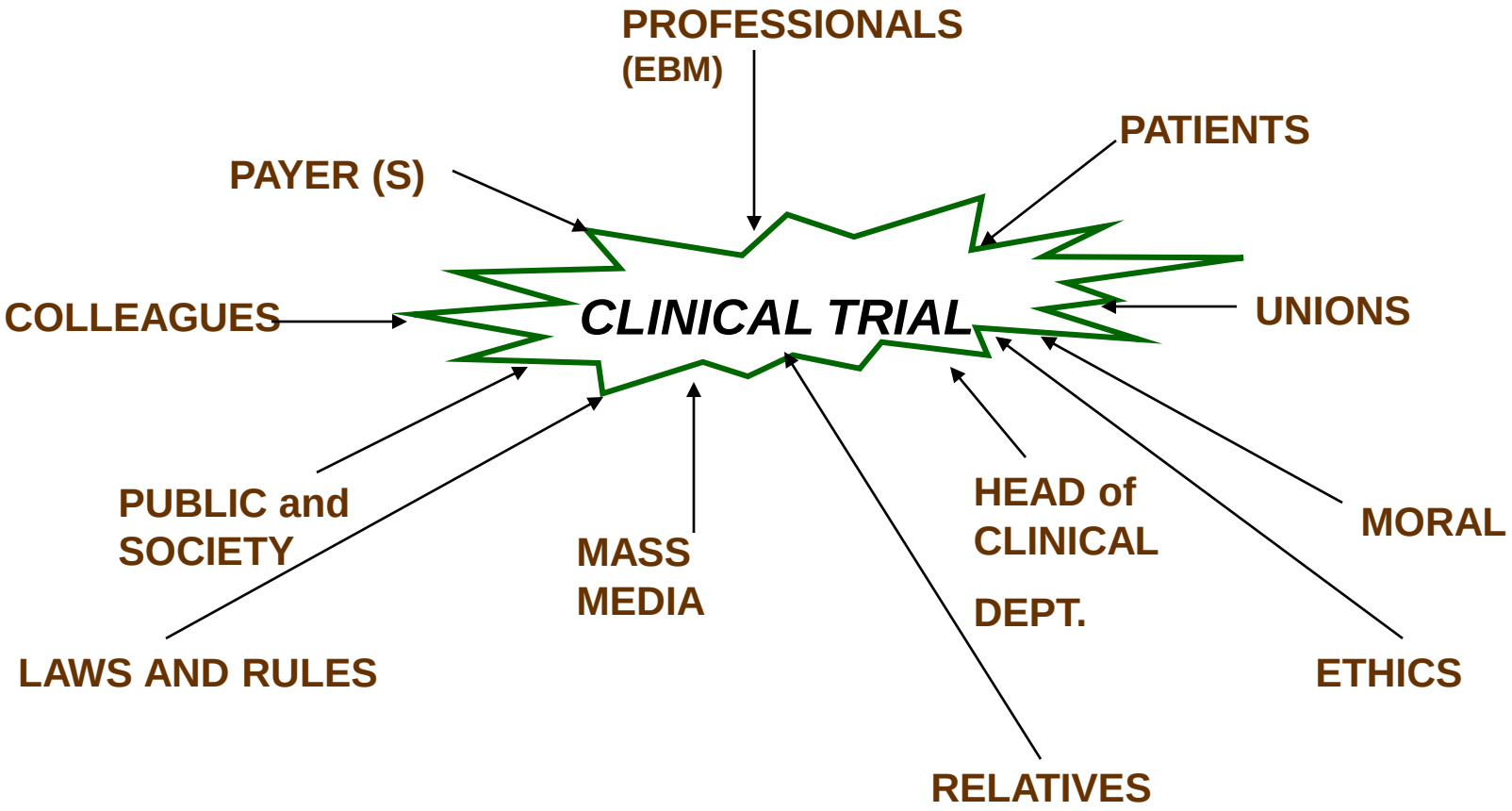


Samma dos till alla patienter...



eller individuell dosering?

INTERESTS


PROFESSIONALS
(EBM)
PATIENTS
PAYER (S)
COLLEAGUES
CLINICAL TRIAL
UNIONS
PUBLIC and
SOCIETY
MASS
MEDIA
HEAD of
CLINICAL
DEPT.
MORAL
LAWS AND RULES
ETHICS
RELATIVES

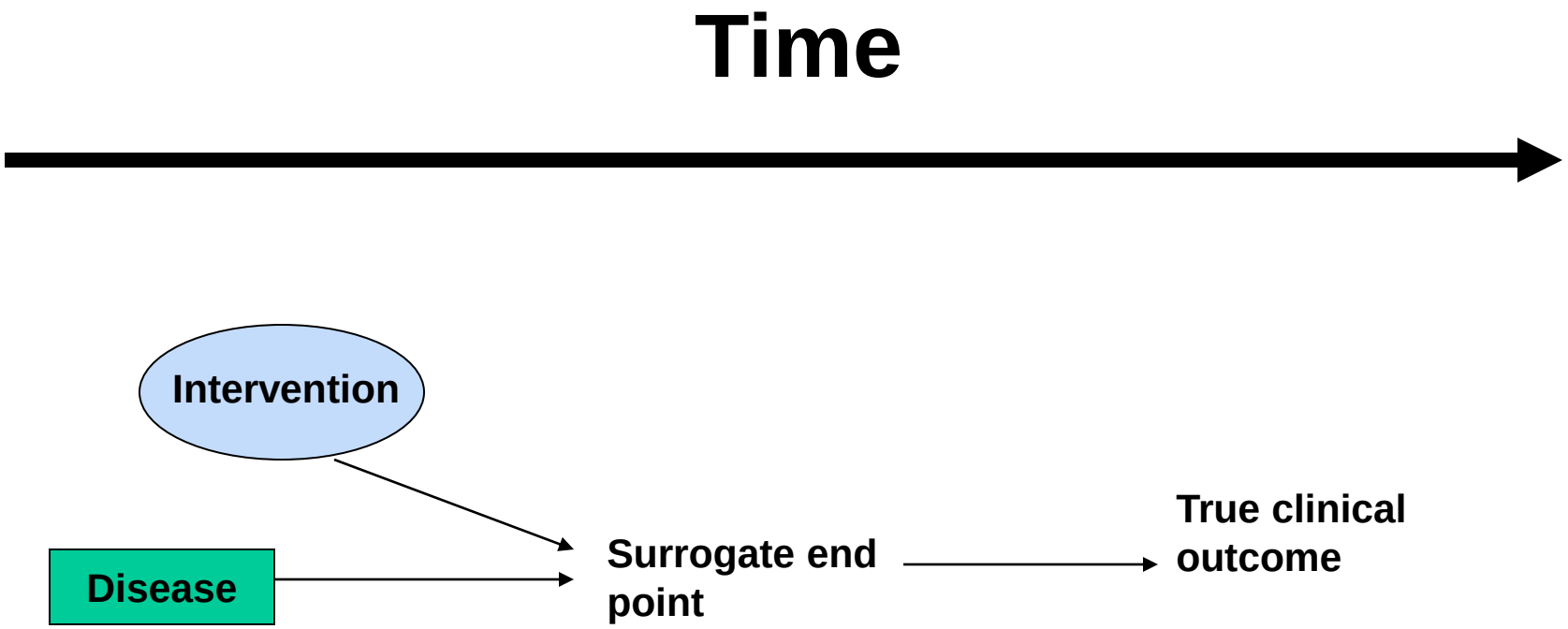


Fig 1 The setting that provides the greatest potential for the surrogate end-point to be valid. Reproduced from (13), with kind permission from the publisher.

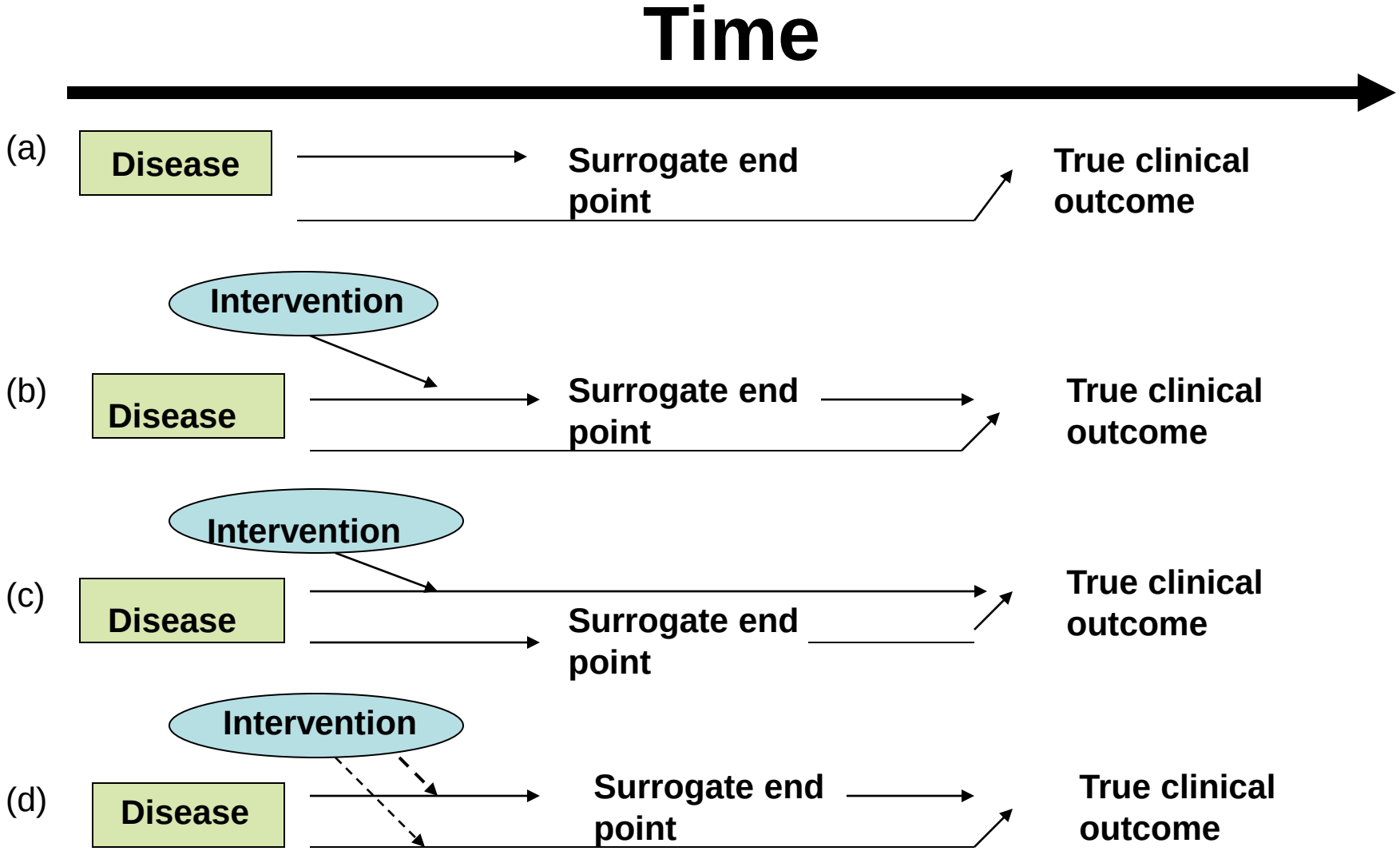


Fig 2. Reasons for failure of surrogate end-points. (a) the surrogate is not in the causal pathway of the disease process. (b) Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate. (c) The surrogate is not in the pathway of the intervention´s effect or is intesitive to its effect. (d) The intervention has mechanisms for action independent of the disease process. Dotter lines = mechanisms of action that might exist. Reproduced from (13), with kind permission from the publisher.

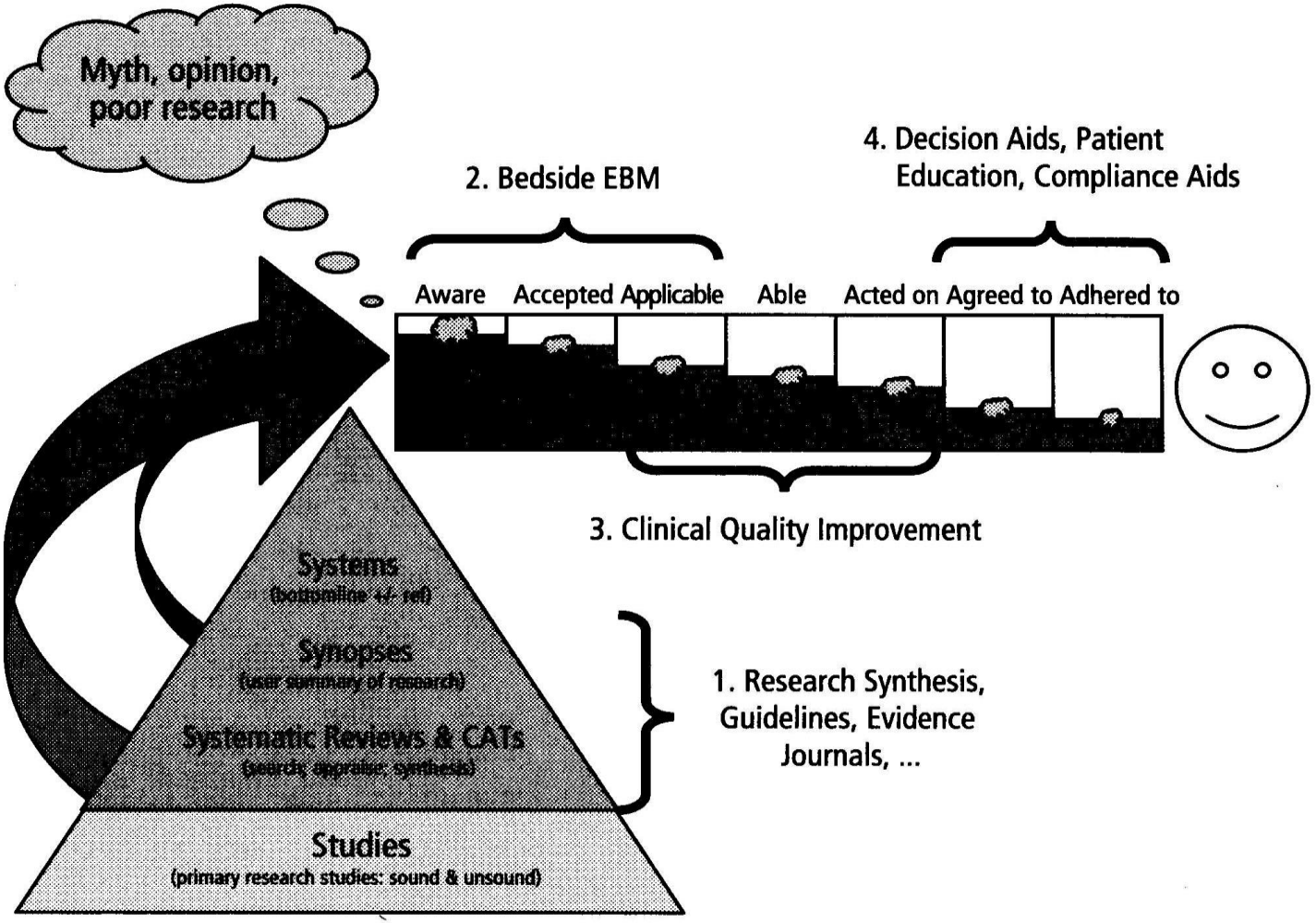


Figure. The research-to-practice pipeline. New research, of varying soundness, is added to the expanding pool and enters practice both directly or is reviewed, summarized, and systematized (delay) before entering practice. Leakage occurs at each of several stages between awareness and patient outcome. Different knowledge translation disciplines focus on different parts of the pipeline (1-4).

FACTORS AFFECTING SELECTION FOR TREATMENT.

Evidence based medicine

Patient demand

Urge to do something

Influence by advertisement

SCIENTIFIC REASONS FOR SELECTION.

RCT

CT

CASE REPORTS

a pp2b: OH3

SEPARATE EPIDEMIOLOGY FROM CLINICAL TRIALS.

Epidemiology presents frequencies and relations.

Clinical trials describes the effect of an intervention.

Patient selection from RCT

Inclusion criterias

Exclusion criterias

AVOID ADVERSE EVENTS.

Interactions.

Doses.

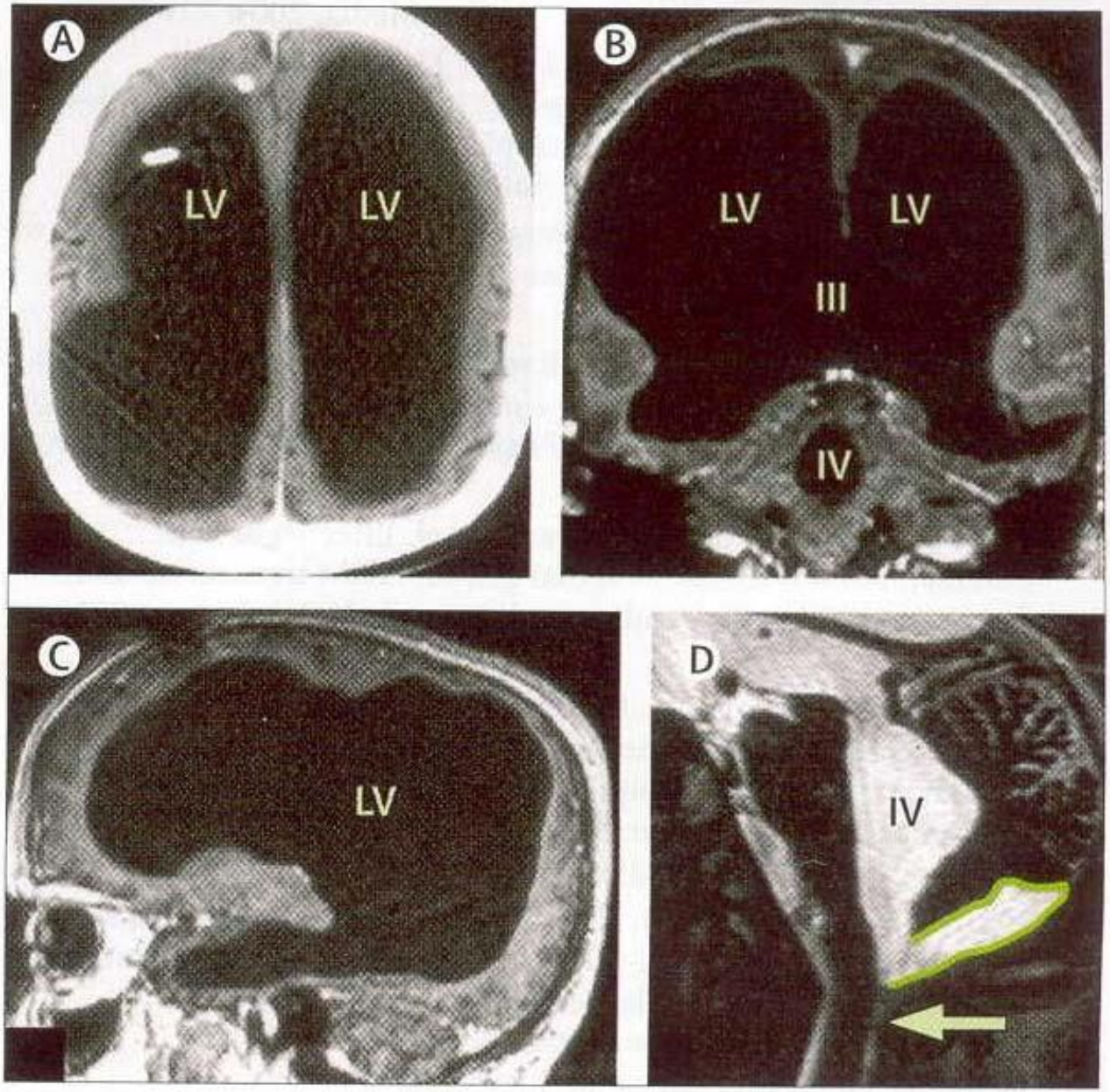
Clinical pharmacology.

HARVARD LAW

UNDER THE MOST RIGOROUSLY CONTROLLED CONDITIONS OF PRESSURE, TEMPERATURE, VOLUME, HUMIDITY AND OTHER VARIABLES,

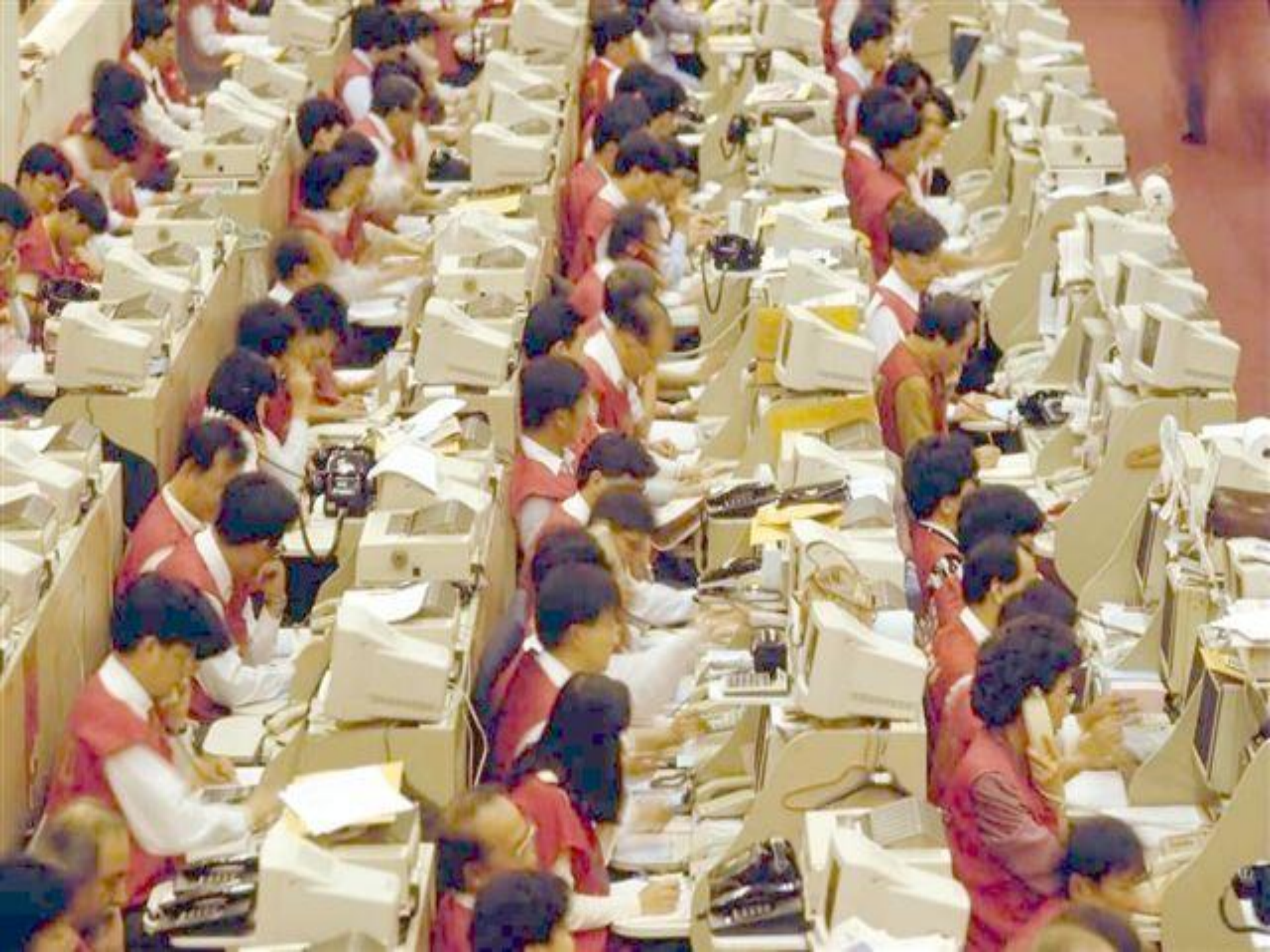
THE ORGANISM WILL

DO AS IT DAMN WELL PLEASES


A
LV
LV
B
LV
LV
III
IV
C
LV
D
IV

Paradigms in learning

Old	New
• Knowing what you should know	• Knowing what you don´t know (not feeling bad about it) and knowing how to find out (or help others to...)
• Much learning ”complete” at the end of formal training	• Learning from cradle to grave (lifelong learner)
• Uncertainty discouraged and ignorance avoided	• Legitimising uncertainty, learning by questioning
• Learning by humiliation; name, shame and blame	• Able to question received wisdom
• Sole methods: apprenticeship, learning from accepted wisdom	• Turning problems into questions to find, appraise, store and act on experience and evidence to solve them
• Finite amount of knowledge to be absorbed	• Complementing experience with knowledge from research
• Intuition very poweful	• Problem and process based learning
• Dominated by knowledge from experience	• Professionals on tap
• Fact and content based learning	
• Professionals on top	



EVIDENCE BASED MEDICINE

IS

THE CONSCIENTIOUS, EXPLICIT, AND JUDICIOUS USE OF CURRENT BEST MEDICINE IN MAKING DECISIONS ABOUT THE CARE OF INDIVIDUAL PATIENTS.

The practise of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

.

EBM – PHILOSOPHICAL ORIGINS EXTEND BACK TO MID-19th CENTURY PARIS AND EARLIER.

EVIDENCE BASED MEDICINE

DECISION MAKING

1. ASKING answerable questions.

2. ACCESSING the best information.

3. APPRAISING the information for validity and relevance.

4. APPLYING the information to patient care.

EVIDENCE BASED MEDICINE

DECISION MAKING

1. ASKING answerable questions.

Accept that you may not know.

Framing the question.

a. A **population** with a clinical problem
b. An **intervention** or exposure
c. The **comparator** intervention or exposure
d. The **outcomes**

Aetiology, prognosis, diagnosis or intervention.

- WHY ME ?
- WHAT´S WRONG WITH ME ?
- WHAT WILL HAPPEN TO ME ?
- HOW WILL INTERVENTION CHANGE OUTCOME ?

EVIDENCE BASED MEDICINE

DECISION MAKING

1. **ASKING answerable questions.**

2. **ACCESSING the best information.**

Summarized primary research – evidence based guidelines and systematic reviews.

- Information is valid
- Relevant (clinically applicable
- Comprehensive
- User-friendly

Primary research-if quality summarised research is not available.

EVIDENCE BASED MEDICINE

DECISION MAKING

1. **ASKING answerable questions.**

2. **ACCESSING the best information.**

3. **APPRAISING the information for validity and relevance.**

Why quality assessment is needed
Poor quality overestimate by 30 %.

Tools for critical appraisal.
How strong is the evidence ?
How big is the effect ?
Does the effect matter to patients ?

EVIDENCE BASED MEDICINE

DECISION MAKING

1. **ASKING answerable questions.**

2. **ACCESSING the best information.**

3. **APPRAISING the information for validity and relevance.**

4. **APPLYING the information to patient care.**

- Make a balance sheet of the benefits and harms of intervention.
- Quantify the likelihood of benefits and harms in relative terms.
- Convert the relative benefits and harms into absolute terms for your patient (using patient characteristics).
- Decide whether the benefits outweigh the harms.

JC Craig et al
Medical Journal of Australia 2001; 174; 248-253

EVIDENCE BASED MEDICINE

>12 000 RCTs PUBLISHED EVERY YEAR

ALREADY TEN YEARS AGO YOU NEED TO READ 17 ARTICLES A DAY EVERY DAY OF THE YEAR – to keep up.

EVIDENCE BASED MEDICINE

Hierarchy of evidence for evaluating a therapy.

Systematic review of several large RCTs.

Single large RCT.

Systematic review of several small RCTs.

Single small RCT.

Systematic review of several cohort studies.

Single cohort study.

Systematic review of several case-control studies.

Single case-control study.

Systematic review of several cross-sectional studies.

Single cross-sectional study.

Case series.

P.J. Devereaux & S. Yusuf, J Intern Med 2003;254;105-113

EVIDENCE BASED MEDICINE

Is this evidence about prognosis valid ?

1. **Was a defined, representative sample of patients assembled at a common (usually early) point in the course of the disease ?**

2. **Was patient follow-up sufficiently long and complete ?**

3. **Were objective outcome criteria applied in a "blind" fashion ?**

4. **If subgroups with different prognoses are identified :**

- **Was there adjustment for important prognostic factors ?**
- **Was there validation in an independent group of "test-set" patients ?**

EVIDENCE BASED MEDICINE

Are the results of this single study valid ?

1. **Was the assignment of patients to treatment randomized?**

2. **Was the randomization list concealed ?**

3. **Were all patients who entered the trial accounted for at its conclusion ? - and were they analyzed in the groups to which they were randomized ?**

4. **Were patients and clinicians kept “blind” to which treatment was being received ?**

5. **Aside from the experimental treatment, were the groups treated equally ?**

6. **Were the groups similar at the start of the trial ?**

ERRARE HUMANUM

EST

SED IN ERRORE

PERSEVERARE TURPE

It is human to be wrong but disgusting to stay wrong

EVALUATION of LITTERATURE

1. Article – Publication – impact factor
2. Main hypothesis
3. Method of intervention
4. Study design
5. Recruitment of patients – inclusion criterias
6. Exclusion criterias
7. Comparability of groups
8. Time of treatment
9. Time of follow-up
10. Number of patients – Start – End
11. Results – clinical significance
12. Side effects/Risks/Complications
13. Judgement and quality
14. Bottom line

90% Blå
10% Röda

24% Röda

4% Röda

MANUSCRIPT QUALITY ASSESSMENT INSTRUMENT 1(4)

Introduction

1. How clear are the background and rationale for this study?

   The frequency and severity of the clinical problem, what remains unknown about the research question, and how patients could benefit from the answer.

2. How clear are the specific aims of this study?

   The research questions (distinguishing main from secondary) and, if appropriate, hypotheses about what will be found.

Methods: *Subjects* *2(4)*

3. How adequate is the description of the setting of the study and source of subjects?

   To help readers understand whether the patients in the study are like theirs, the manuscript should provide information on when and where the research took place, a description of the level of care (community, primary care, referred), and if patients were referred, the pattern (source, distance, route) of referral.

4. How clear are the eligibility (inclusion and exclusion) criteria.

5. For studies in which two groups are compared, is there enough information to judge the suitability of the comparison groups?

   How well was it reported how patients were chosen (for observational studies) or selected (for experiments) so that readers can judge whether the researchers have compared like with like?

Methods: *Design*

6. How clear is the study design?

   Do you understand what the authors set out to do and how they did it (the study design)?

7. How adequate is the description of the masking (i.e. Blinding) procedure?

   Is it clear who was blinded, what blinding procedure was used, and the degree to which blinding was achieved?

Methods: *Variable measurement* *4(4)*

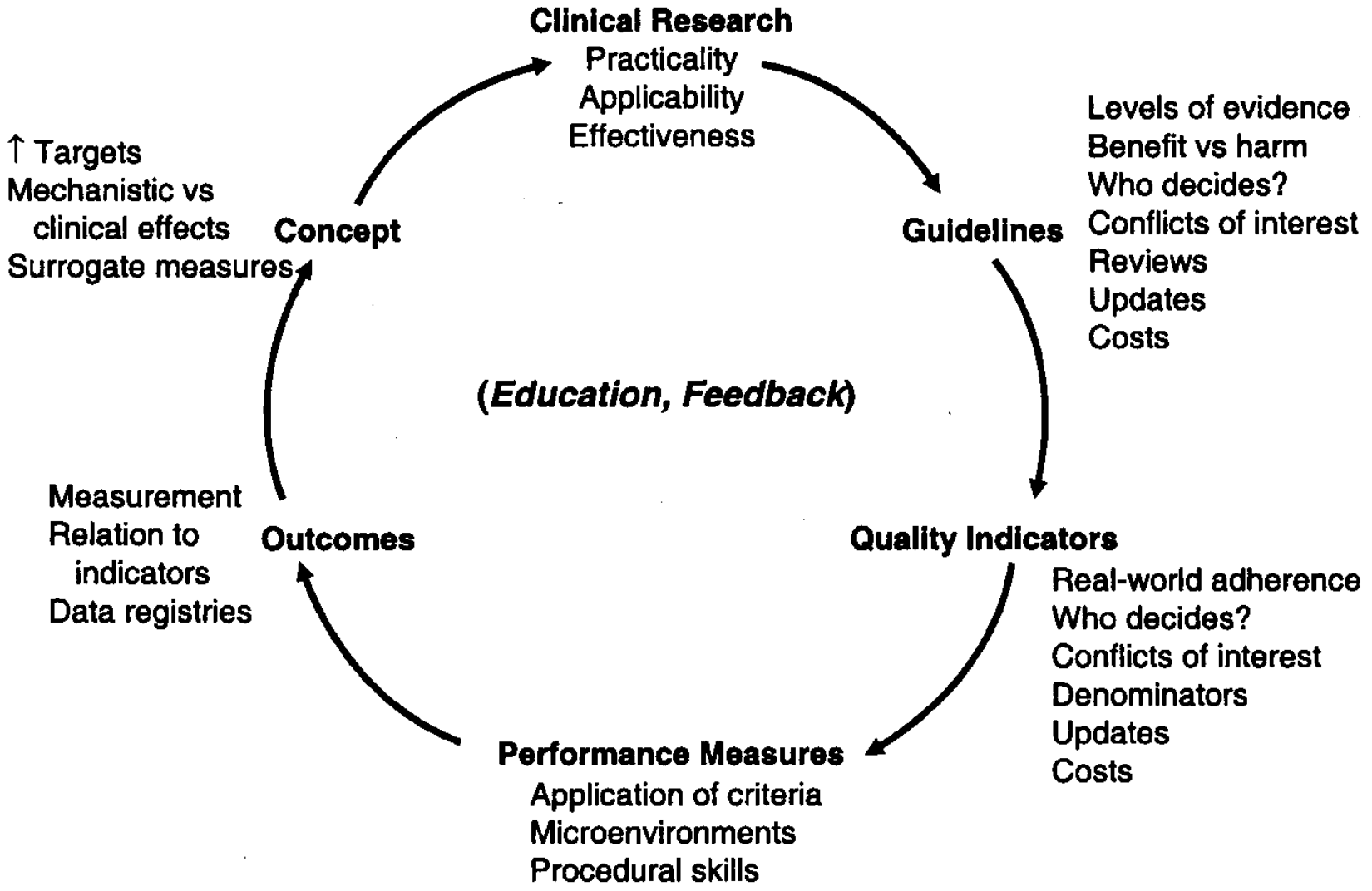
8. Is the operational definition of major variables clear enough so their strengths and limitations can be assessed?

   For example, in surveys, case definitions; in cohort studies, definitions for exposure and disease status; in diagnostic studies, the test procedure; for case control studies, is it clean how cases and controls were defined? Other major variables might include important confounders, compliance, etc.

9. How adequate is the reporting of important side-effects?

   For example, what are the types and numbers?

Fig. 1



Model for the integration of quality into the therapeutic development cycle

Fig. 2

How to implement new knowledge of medicaments in clinical (”daily-life”) practice

A. Evidence based science / RCT

↓

B. Guidelines

C. Implementation

Fig. 3

Evidence-based medicine (RCT) - and ”real life”

Clinical trials	”Real life”
Few elderly patients	Many elderly patients
Few women	Many women
Few drugs	Poly-pharmacy
	Poly-morbidity

Example

Dabigatran vs warfarin in atrial fibrillation

	Event rates	**RRR**	**NNT**
Stroke or systemic embolism	2,2% vs 3,0%	27%	124
Stroke	2,0% vs 2,8%	30%	120
Death	7,2% vs 7,4%	3%	N.S.
Major hemorrhage	6,2% vs 5,4%	16%	N.S.

NEJM 2009; 361: 1139-51

Fig. 4

CHF-treatment – from ”science” to ”clinic reality”

Gaps” between research (EBM) and ”real life”

	”Clinical trials” vs.	”Real life”
Age	60-65 y	> 70-75 y
Male/female-ratio	3-4/1	1/1½
Polyfarmacy	few patients	many patients*)
Polymorbidity	few patients	many patients**) > 40-50%

*) NSAID-medication etc.

**) Diabetes, renal diseases etc.

Fig. 5

Evidence based medicine, treatment guidelines and implementation – what are the limitations?

A. Patient related

B. Doctor related

C. Other explanations

Fig. 6

A. “Patient-related” limitations barriers against guidelines:

- Reluctance against medications
- Risk of side-effect, short- or long-term
- Economy

Fig. 7

B. “Doctor related” limitations - barriers against gudelines:

- Awareness / attention of polypharmacy
- Fear of inducing sickliness in patients
- Not convinced of the drug-effect (NNT)

Fig. 8

C. Other explanations

- Unclear, uncertain guidelines for individual cases
  - no evidence based science

- Attitude towards medications – media / press,
  local hospitals, specialists etc.

Fig. 9

Posibilities for better implementation of guidelines

A. CME

B. Quality securing activities

C. Social influence

D. Direct GP-contact

Fig. 10

A. CME

- Instructions - recommendations
- Symposia, post-graduate education, workshops
- Articles from relevant medical journals

Fig. 11

B. Quality securing activities

- Audit – with feed-back

  Clinical data-bases

  Second opinion / shared care

- Reminders – to GP and / or patients

Fig. 12

C. Social influence

- Campaign's – "patient-related"
- Local opinion-leaders
- Local guidelines

Fig. 13

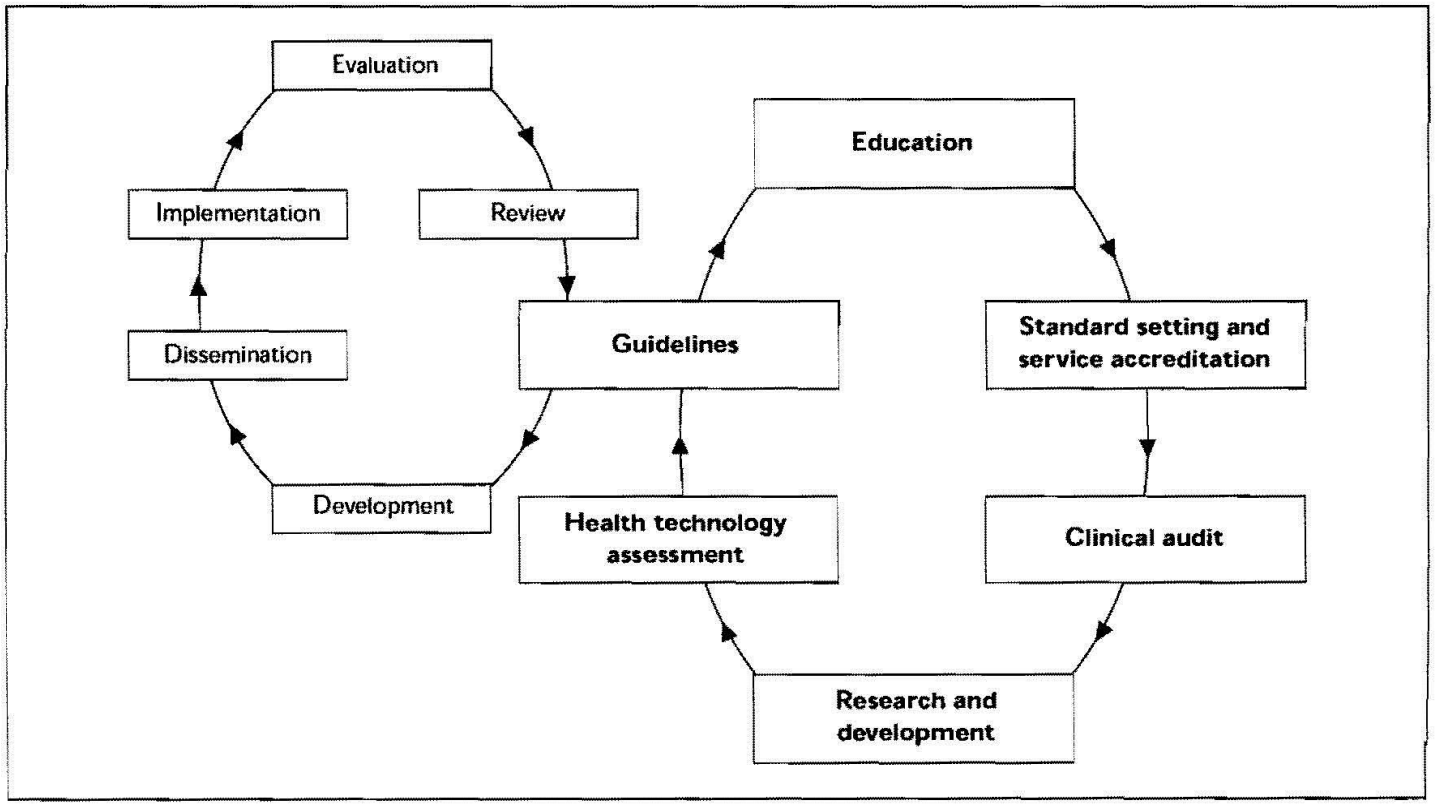
D. Direct GP - contact

- "Medicament – adviser" (industry)

- "Post-graduate training"

12

Fig. 1 Clinical effectiveness cycle.



Scottish Intercollegiate Guidelines Network
28 Thistle Street
Edinburgh
EH2 1EN
The United Kingdom

S Twaddle,
BA, MSc, PhD
Director

Correspondence to:
Dr Sara Twaddle
Tel: (44) 131 718 5090
Fax: (44) 131 718 5114
Email: sara.twaddle@nhs.net

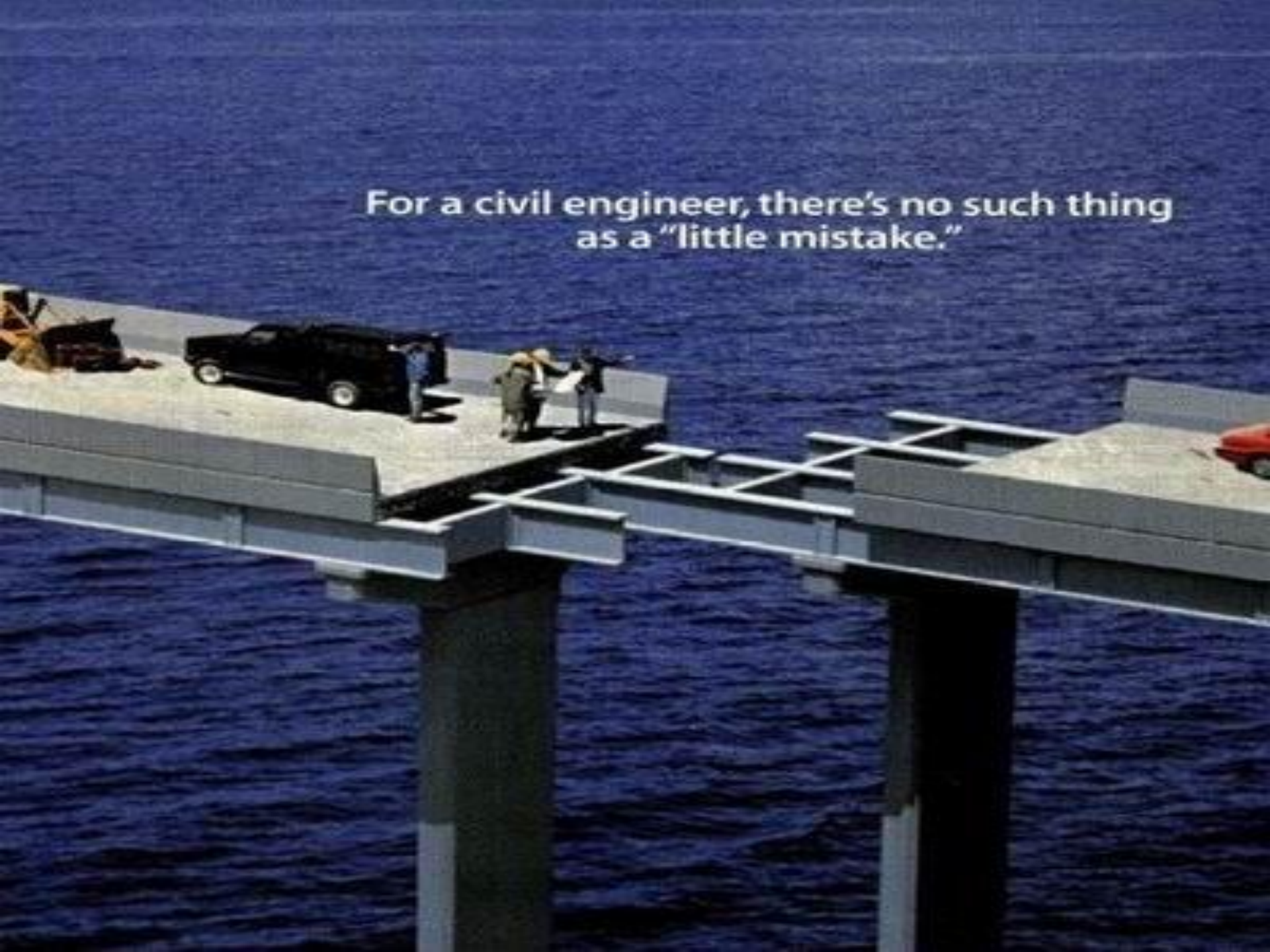
Grades of recommendation

A At least one meta-analysis, systematic review of RCT, or RCT rated as 1++, and directly applicable to the target population; or
A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+.

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++.

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+.


For a civil engineer, there's no such thing
as a "little mistake."

The End

VAD VÄRDERAS I EN FORSKNINGSANSÖKAN?

1. **Medicinskt – vetenskapligt**
   - relevant frågeställning?
   - intressant kunskapsmässigt?
   - intressant sjukvårdsmässigt?
2. **Vetenskapliga förmågan i projektet**
   - finns kompetensen?
   - är metodiken adekvat?
   - räcker kliniska materialet?
3. **Förutsättningarna**
   - finns kringpersonal, lab-utrymmen, miljön, datorer m m.?
   - är ekonomin rimlig? (grundantagande – nej!)

OM JOURNALEN - JOURNAL FR DAGBOK, ORDBOK FÖR LÖPANDE ANTECKNINGAR, LIGGARE, TIDSKRIFT

SYFTEN

1. Läkarens arbetsverktyg
2. Informationskälla för patienten
3. Instrument för Kvalitets – Uppföljnings – och Utvärderingsarbete
4. Underlag för tillsyn och kontroll
5. Underlag för FoUU-verksamhet

Skall innehålla: ANAMNES, STATUS, DIAGNOS, PROGNOS
”dokumentation mer av planlös välvilja än av målinriktat arbete”

ATT SKRIVA FORSKNINGSANSÖKAN 1(2)

1. **PROJEKTTITEL**
   - ger en bild av frågeställningen i sitt sammanhang
   - medverkande personer i hela projektet
2. **FRÅGESTÄLLNING**
   - klar och enkel, helst en enda mening
3. **BAKGRUND**
   - vad vet vi idag inom området? vad finns publicerat? gärna med en kort (5-10) aktuell referenslista
   - hur blev jag inblandad i detta?
   - vad kännetecknar min ”forskningsmiljö” som gör att jag intresserar mej för detta och tror att jag kan lösa frågeställningen?

ATT SKRIVA FORSKNINGSANSÖKAN 2(2)

4. METODIK

- metoder beskrivs, inkl laboratoriemetodiker och om de finns eller skall sättas upp
- kompetens på medverkande personal ex lab biträde, sköterska

5. BETYDELSE

- gärna något mer än att den är ”oerhörd”. Tänk efter ”Varför längtar världen efter att få veta svaret på frågeställningen”; (kan vara för att förstå något annat eller komma vidare i en frågeställning, belysa från annan synvinkel).

6. PLANERING AV PROJEKTET

- arbetskraft finns? Lokaler?
- tidsplan
- detaljerad budget för personal (lön och LKP) och material (glöm inte ev statistikerhjälp, databearbetning, sekreterarhjälp)
- andra ekonomiska källor eller ansökningar

VÄGLEDNING FÖR KVALITET

1. **Rodogörelse för ALLA randomiserade patienter**

2. **Klar och tydlig ”outcome”**

3. **Skötsel av patienter i studien**
   - **diagnostik**
   - **samtidig behandling**
   - **compliance**
   - **adverse events**

KOSTNADER FÖR DÅLIG KVALITET ÄR ENORM

GÅR MAN VILSE
TILLRÄCKLIGT LÄNGE
BÖRJAR MAN KÄNNA
SIG HEMMA.

DICK
LIVET BESTÅR INTE BARA
AV FÖRTRETLIGHETER.
DET FINNS EN MASSA
REJÄLT HELVETE OCKSÅ.

PROBLEM – FRAMTIDA KLINISKA PRÖVNINGAR

1. Höga kostnader
2. Samla inte endast indata utan designa bästa studien och analysera data för att lösa hälsoproblem
3. Kliniska prövare är inte adekvat utbildade
4. Etiska– och regelstrukturen är komplexa, dåligt organiserade och av okänt värde
5. Frågeställningarna i kliniska prövningar är inte de som läkare och sjukvårdshuvudmän mest behöver
6. Stora svårigheter i att överföra forskningsresultat till praktisk sjukvård
7. Kunskapsförmedlingen mellan klinisk forskning – sjukvård och allmänhet skapar luckor

SBU
FETMA – PROBLEM OCH ÅTGÄRDER.

Rapport nr 160,200

EVIDENSSTYRKA 1.

Starkt vetenskapligt underlag. Minst två studier med högt bevisvärde eller en god systematisk översikt.

EVIDENSSTYRKA 2.

Måttligt starkt vetenskapligt underlag. En studie med högt och minst två studier med medelhögt bevisvärde. Inget väsentligt talande emot fynden.

EVIDENSSTYRKA 3.

Begränsat vetenskapligt underlag. Minst två studier med medelhögt bevisvärde. Inget väsentligt talande emot fynden.

SBU
FETMA – PROBLEM OCH ÅTGÄRDER.

Rapport nr 160,2002

GRANSKNING

Studierna skulle behandla fetma dvs BMI > 30.

Studiernas uppföljningstid skulle vara minst 12 månader.

Kontrollgrupp måste finnas.

Studien måste innehålla någon relevant resultatvariabel.

Rapporter om biverkningar och risker eftersöktes särskilt.

Hälsoekonomiska utvärderingar enligt särskilt redovisade kriterier.

SBU
FETMA – PROBLEM OCH ÅTGÄRDER.
Rapport nr 160,2002

KVALITETSBEDÖMNING

STUDIETYP.

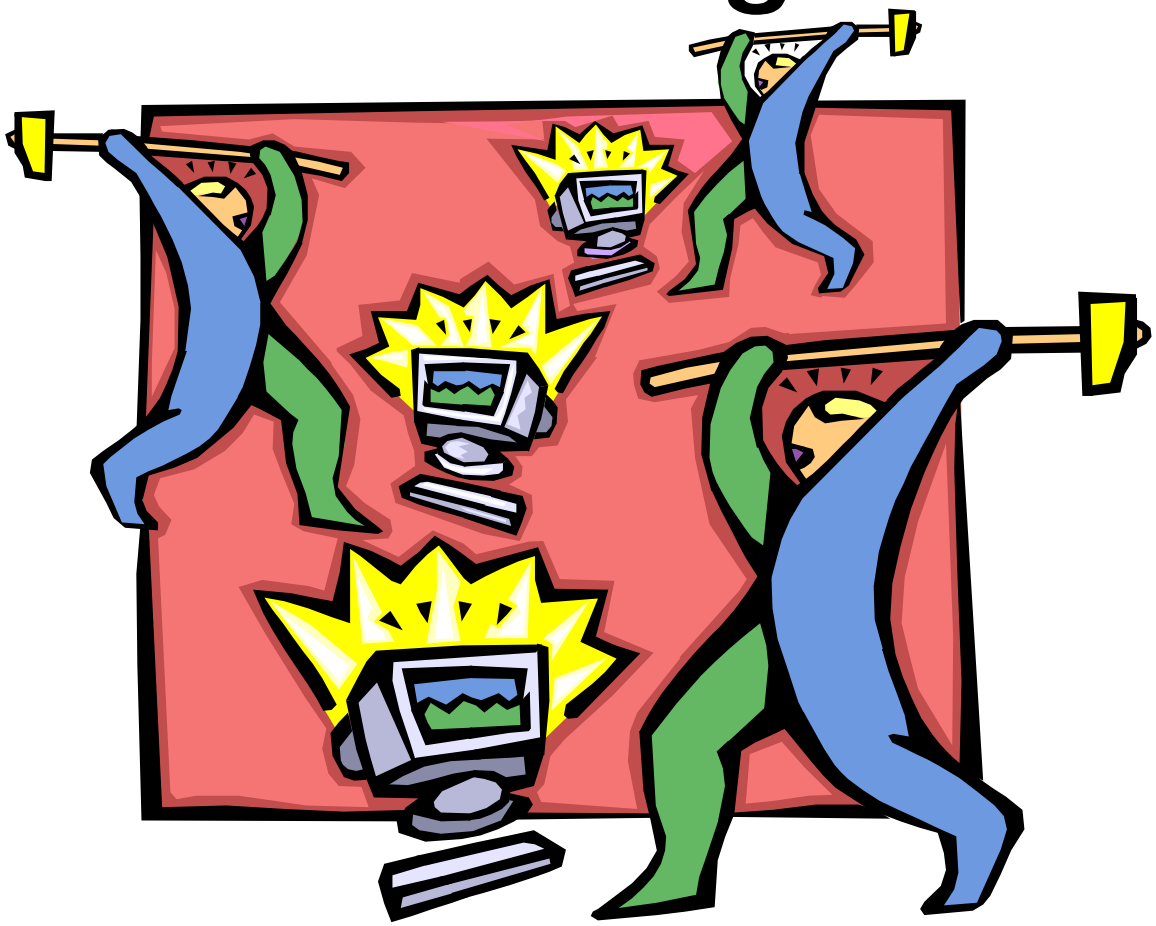
UPPFÖLJNINGSTID.

BORTFALLETS STORLEK.

STUDIENS STORLEK – ANTAL UPPFÖLJDA PATIENTER.

PREVENTIONSSTUDIER.

Barking up the wrong tree



THOSE who think

They know it all

Are very annoying

To those of us

WHO DO

YOU THINK YOU'VE GOT A BAD JOB???

AND MY PERSONAL FAVOURITE...

Grades of recommendation

A At least one meta-analysis, systematic review of RCT, or RCT rated as 1++, and directly applicable to the target population; or
A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+.

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++.

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+.