



Health Technology Assessment for future generations

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What is HTA?

“HTA involves the medical, social, ethical and economic implications of the development, diffusion and use of a health technology. HTA has been positioned as a ‘bridge between scientific evidence and the needs of policymakers”



HTAi definition of HTA

- *A research-based ,practice-oriented assessment of relevant available knowledge on the direct and intended consequences of technologies ,as well as the indirect and unintended consequences. The goal of health technology assessment is to provide input to decision making in policy and practice*

HEALTH TECHNOLOGY ASSESSMENT



- The major aim of health technology assessment for registration is to provide consumers with safe and effective drugs
- The major aim of assessment for subsidy is to ensure that the cost effectiveness of a drug represents “value for money” taking into account opportunity costs

CONTEXT OF THE ASSESSMENT FOR THE CONSUMER

- A therapeutic option decision might be very much influenced by the comparison of studies using placebo as comparator relative to those using an active comparator which may be a treatment option. The comparative risk/benefit/cost options may be different in the two scenarios.



Registration versus Subsidy

- "...so there is an increasing obligation for the developers of new treatments to provide evidence on a broader range of questions and outcomes in addition to the efficacy and safety data required by licensing authorities"



What are we assessing?

- Can it work (efficacy)?
- Does it work (effectiveness)?
- Is it worth it (cost effectiveness)?



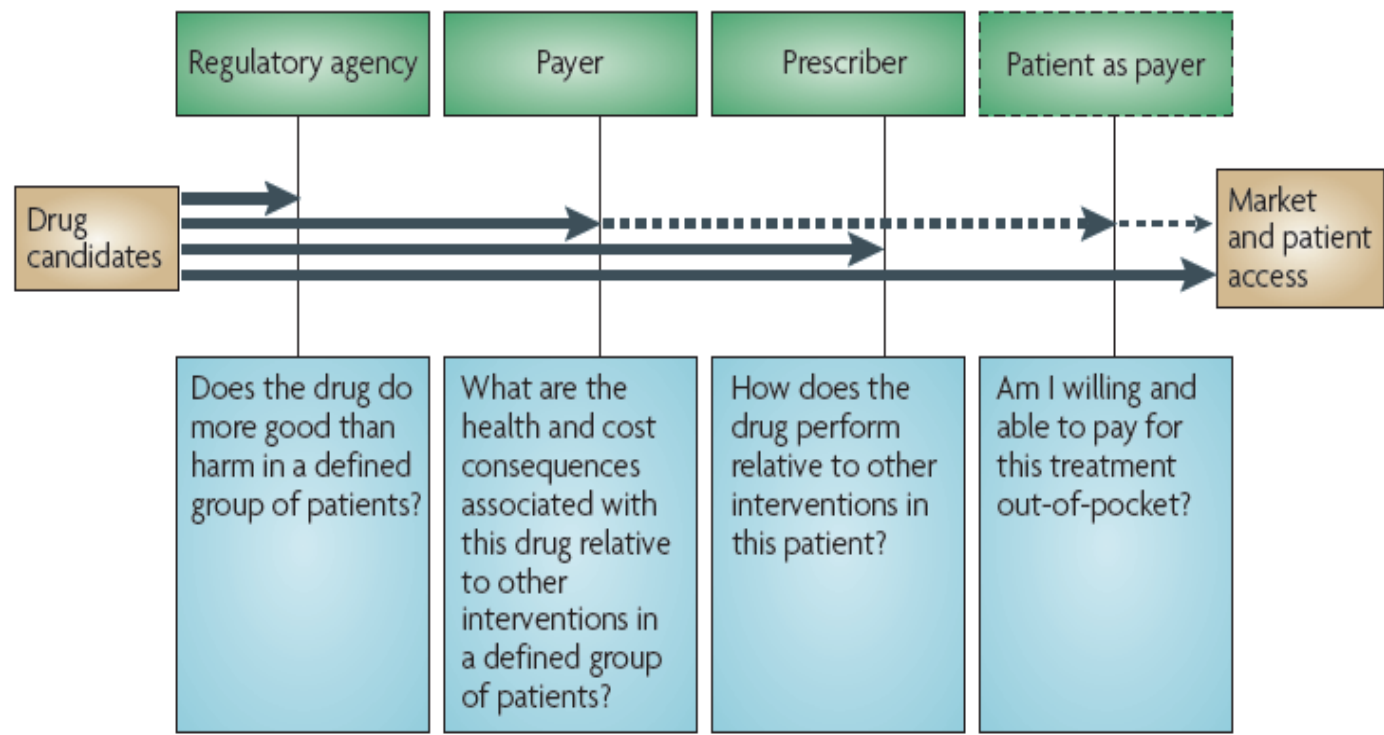
When can these questions be answered?

Clearly these questions are never answered absolutely because they are context and time-dependent

Assessment should be a continuum from discovery to oblivion

Market Access

Eichler et al Nature Reviews 2011





Working Definitions

- ***Efficacy***: the extent to which an intervention does more good than harm under ideal circumstances
- ***Relative Efficacy***: the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternatives



Working Definitions

- ***Effectiveness***: the extent to which an intervention does more good than harm when provided under usual circumstances of health care practice
- ***Relative effectiveness***: the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice



Jarvinen et al BMJ 2011

- “Evidence of efficacy is only the first step in the process of assessing whether a healthcare intervention is appropriate for wider clinical use. Even if an intervention is successful in a study, it may not succeed similarly in usual care...”
- “It is wrong to assume that efficacy results apply faithfully in clinical practice

So you have a trial?

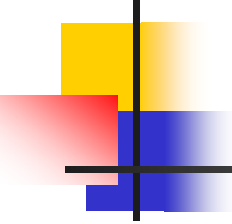


- Is it relevant for all HTA Agencies?
- Does it inform clinical practice?
- Is it relevant to patients ?
- What is the degree of uncertainty?
- etc

Trial versus Clinical Setting

APPLICABILITY

- The participants and circumstances of use in a trial may not be the same as the proposed population for treatment (and might therefore have different expected risk) .The results have to be **APPLIED** to the proposed population and expected risk eg the severity of the disease in the patients in the trial, prior exposure to other therapies etc



A medicine may be less effective than predicted from clinical trials because ..

- the intrinsic property of the medicine itself in the population exposed eg longer term toxicity, the medicine was used in patients whose benefit was less than in the those in the efficacy trials eg used in those whose absolute risk was lower
- The way in which the medicine was used in practice eg QUM issues-compliance, drug interactions, patients with co-morbidities etc

Adverse influences on the generalisability of the results of RCTs*

Factors	Issues	Potential problems
Patients	age	Effectiveness in younger or older patients
	Gender	Effectiveness generally
	Molecular pathogenesis	Need to target
	Disease Severity	Effectiveness in milder or severer forms of the condition
*M Rawlins The Harveian Oration of 2008		

Adverse influences on the generalisability of the results of RCTs*

Factors	Issues	Potential problems
Patients	Risk Factors	Effectiveness in patients with risk factors for the condition
	Co-morbidities	Influence of other conditions on effectiveness
	Ethnicity	Effectiveness in other ethnic groups
	Socio-economic status	Effectiveness in disadvantaged groups

*M Rawlins
The
Harveian
Oration of
2008

Adverse influences on the generalisability of the results of RCTs*

Factors	Issues	Potential problems
Treatment	Dose	Too high dose used in RCTs
	Timing of dosing	Influence of adherence (compliance)
	Duration of Therapy	Effectiveness during long term use
	Co-medication	Adverse interactions
	Comparative Effectiveness	Comparison with other treatment options
Setting	Quality of care	Prescription and monitoring by less specialist healthcare providers
*M Rawlins The Harveian		

Applicability of Trial Data

- Are there applicability issues relating to patient selection and the population in whom subsidy is proposed?. An increasing number of pivotal trials are being conducted in Asian countries particularly China and India. What are their relevance to other populations?
- Can we predict outcome and toxicity modifiers?.
- Is genetic polymorphism relevant?.
- Is the molecular basis of the disease consistent across populations.



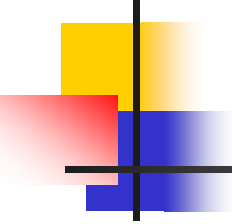
Applicability of Trial Data

- Is the standard of care similar in multi-centre trials?
- Example with the clinical outcome of Gefitinib in NSCLC in Japanese/non-Japanese patients and the comparative efficacy between warfarin and dabigatran in AF in various countries depending on the standard of care-Does this have implications for large multicentre trials

Trial versus Clinical Setting

EXTRAPOLATION

- The length of follow-up of participants in the trial may be less than the expected duration of treatment .Results may need to be **EXTRAPOLATED** to the proposed duration of treatment (eg 6 week trial of an antidepressant, extrapolation of survival beyond the duration of the trial)



Trial versus Clinical Setting

TRANSFORMATION

- The outcomes measured in the trial might not be the patient-relevant outcomes of treatment. Results generated in this way need to be **TRANSFORMED** to take account of patient-relevant final outcomes (eg QALY)
 - eg use of surrogate outcomes, progression free survival etc



TRANSLATION

- Therefore the results of trials need to be applied, extrapolated and transformed (collectively referred to as ‘translated”) into a decision analysis appropriate for the proposed clinical use.
- The question remains as to the extent to which the translation is uncertain. It is this uncertainty which drives the utility of post marketing/listing monitoring



What data

- Because of the major issues in translation of trial data to the decision context, there is an urgent need for the relevant factors to be considered as part of a trial design and proposals for post marketing activities not just focusing solely on safety



What Data?

- It has been argued that increasing the size of trials and their complexity and always conducting randomised trials which includes an active comparator as well as placebo is required in order to address the issue of translation from clinical data to clinical use

OR

- Smaller trials designed to detect only what is considered to be patient relevant improvements



What data-what is the impact?

- Larger trials in order to detect small differences between actives
- Impact on the patient pool particularly for orphan diseases
- More expensive trials
- Longer trials



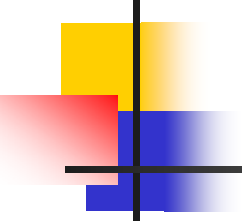
When are “positive” clinical trials in Oncology Truly Positive

- Ocana and Tannock J Natl Cancer Inst 2011
- *“We suggest that trials should not be declared positive based only on a statistically significant P value, but should also require detection of a difference in survival outcomes that equals or exceeds a clinically important value that is specified in the protocol”*
- *WHO DEFINES A CLINICALLY IMPORTANT VALUE?*



How much uncertainty is acceptable at the time of the decision?

- What factors should be considered in addressing this issue?
- Eg severity of disease, access to effective alternatives, place in therapy
??????????????

- 
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- If we have uncertainty-which we always will have to varying degrees-then clearly a clinical trial is only the start of the process



Health Technology Assessment- History, fixed viewpoints or progress?

- 'If you find that a study was not randomized, we'd suggest that you stop reading it and go on to the next article"

*Sacket et al Evidence-based
medicine;how to practice and teach
EBM .Churchill Livingstone 1997*

Sir Michael Rawlins-Harveian Oration 2008

- “Randomised controlled trials (RCTs), long regarded as the “gold standard” of evidence have been put on an undeserved pedestal. Their appearance at the top of “hierarchies” of evidence is inappropriate ; and hierarchies themselves are illusory tools for assessing evidence”

Sir Michael Rawlins-Harveian

Oration 2008

- “Hierarchies attempt to replace judgement with an over-simplistic, pseudo-quantitative assessment of the quality of the available evidence”

Sir Michael Rawlins; Harveian Oration 2008



- ...arguments about the relative importance of different kinds of evidence are an unnecessary distraction. What is needed instead is for 'investigators to continue to develop and improve their methodologies; for decision makers to avoid adopting entrenched positions about the nature of evidence; and for both to accept that the interpretation of evidence requires judgement"



Where are the methodological gaps?

- There is an urgent need for the development of new methods to analyse data not only post marketing data but also data from randomized trials. We will need to use a multiplicity of trial designs and techniques



Examples of Specific Data issues requiring urgent attention by researchers

- Indirect Comparisons-are active comparator trials necessary-what is the impact of cost, time on access and progress. What is the correct method for analysing indirect comparisons
- Unless all trials have an active comparator we will continue to use indirect comparisons.
- Will network analyses provide less uncertainty



Early Crossover

This is a particular issue in oncology

Ethics committees requiring the option for early crossover even though the specific purpose is to test an hypothesis. The allowance of cross over may in fact compromise the ability to answer the question. There is likely to be significant confounding in crossover design



Early Crossover

- The use of Inverse Probability Weighting or Structure Failure time methodologies have been examined –are they appropriate, what is their reliability and stability? The use of these methods is still uncertain and the limitations of the methods appear not to have been investigated



Examples of Specific Data issues requiring urgent attention by researchers

- Post Marketing data-observational data -how confounded?can we manage confounding? can we analyse data better/smarter? What do we learn from yesterday's symposium?
- Surrogate endpoints-what needs to be done to validate surrogates for regulators and payers-likely to be different for both agencies



Examples of Specific Data issues requiring urgent attention

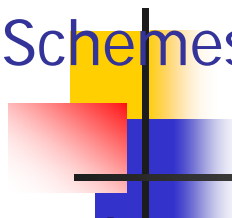
- Minimum clinically significant differences that are patient relevant-what are they and what factors will influence this judgement.



Examples of Specific Data issues requiring urgent attention by researchers

- Measurement of quality of life-which measure?,when?,in whom?
- Bio-markers: -prognostic or treatment effect modifiers?
- Continuation beyond disease progression although trial ceased and no data is available – how can this be monitored?

Post Marketing Surveillance(PMS) and Managed Entry Schemes (MES)



- The regulatory authorities are becoming more interested in post marketing surveillance
- The sponsors want earlier funded access under a coverage with evidence framework
- Are PMS and MES the same ?-if not how do they differ
- Does this whole area need to be considered as a continuum under a common framework-since uncertainty in efficacy and/or safety has a direct impact on uncertainty in cost effectiveness



Managed Entry Schemes

- Where the PBAC identifies a clinical need and is presented with a product which may fulfill that need but the data presented comes with large uncertainty, the product may be recommended for listing (at a price commensurate with the degree of uncertainty) under a managed entry scheme
- The condition is that there is a randomised trial (or other fit-for-purpose data collection) which the PBAC believes will address the areas of uncertainty within a reasonable timeframe. The sponsor must agree to continue supply



HTA for payers and regulators

- Because market authorization is no longer the sole barrier to access and that the payer requirements can be different, we need to examine how trial designs can be amended to address both agencies as efficiently as possible
- Sean Tunis is chairing a group (Green Park Group) of regulators/payers, Industry and consumers to examine this issue for Alzheimers disease.



The QALY or?

Dr P Neumann JAMA May 4 ,2011



- *Experience demonstrates that rigid use of cost-per-QALY thresholds is unacceptable*
- *For all its shortcomings, the QALY provides a helpful benchmark in considerations of comparative value.*

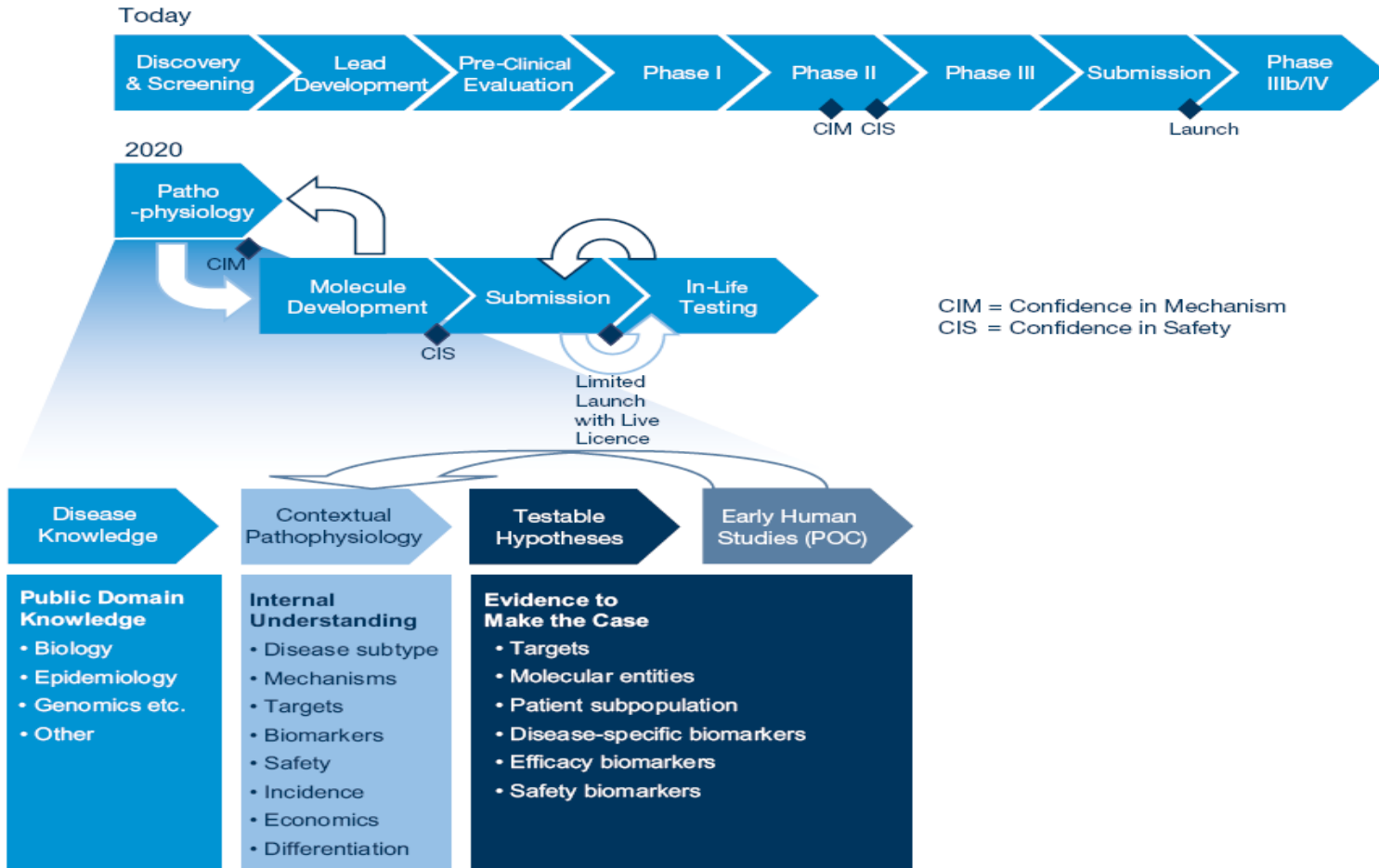
Dr P Neumann JAMA May 4 ,2011



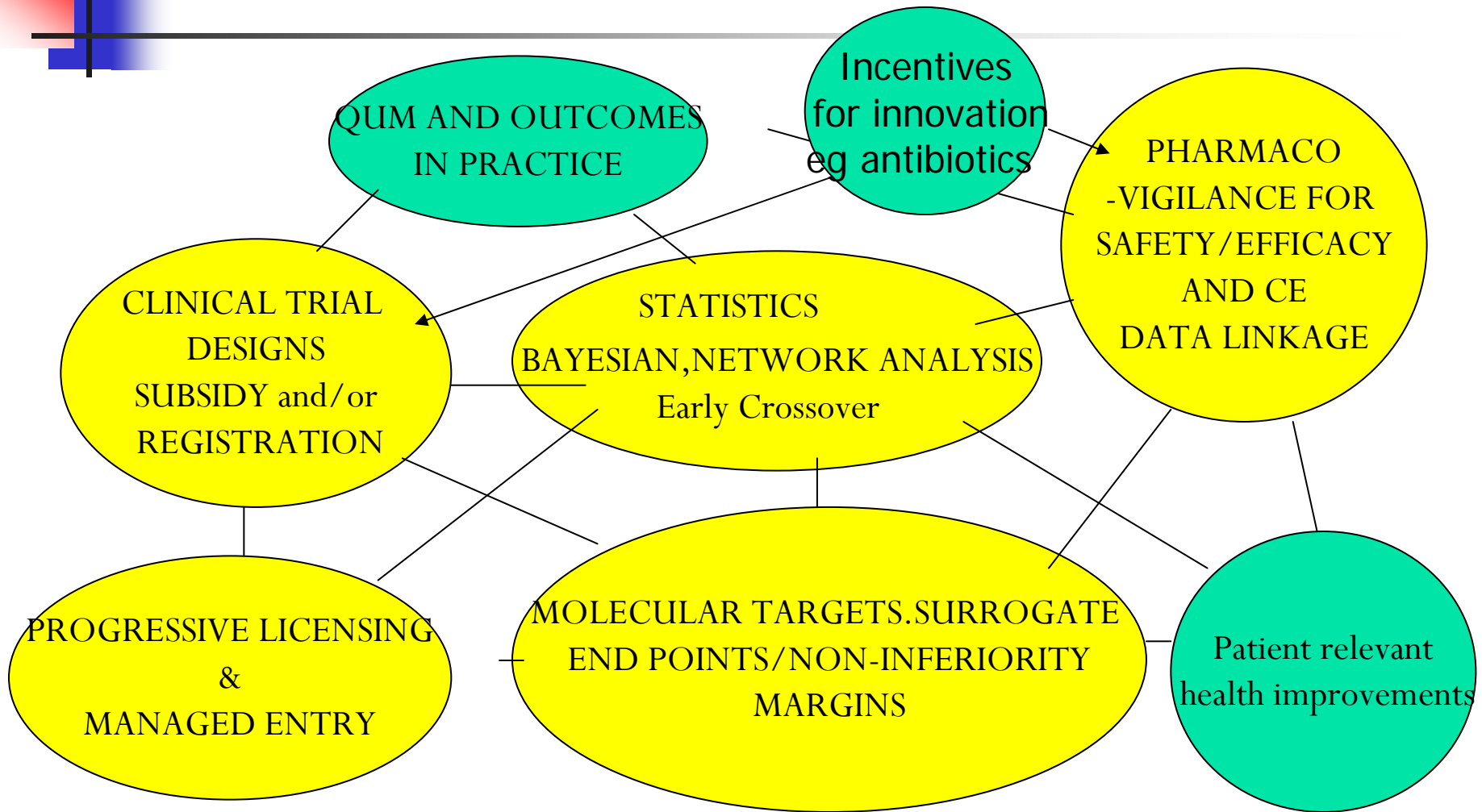
- *Society could attempt to abandon the idea of a common measure and rely solely on disease-specific metrics and expert judgment based on clinical need. However that would not permit comparisons among diseases and conditions or between treatment and prevention*

The R&D process of the future

Pharma 2020 Price Waterhouse Cooper



INTEGRATION





CONSILIENCE —THE KEY TO UNIFICATION (*Wilson E O 1998*)

PHYSICAL AND
BIOLOGICAL
SCIENCES

SOCIAL/FISCAL
ENVIRONMENT POLICY

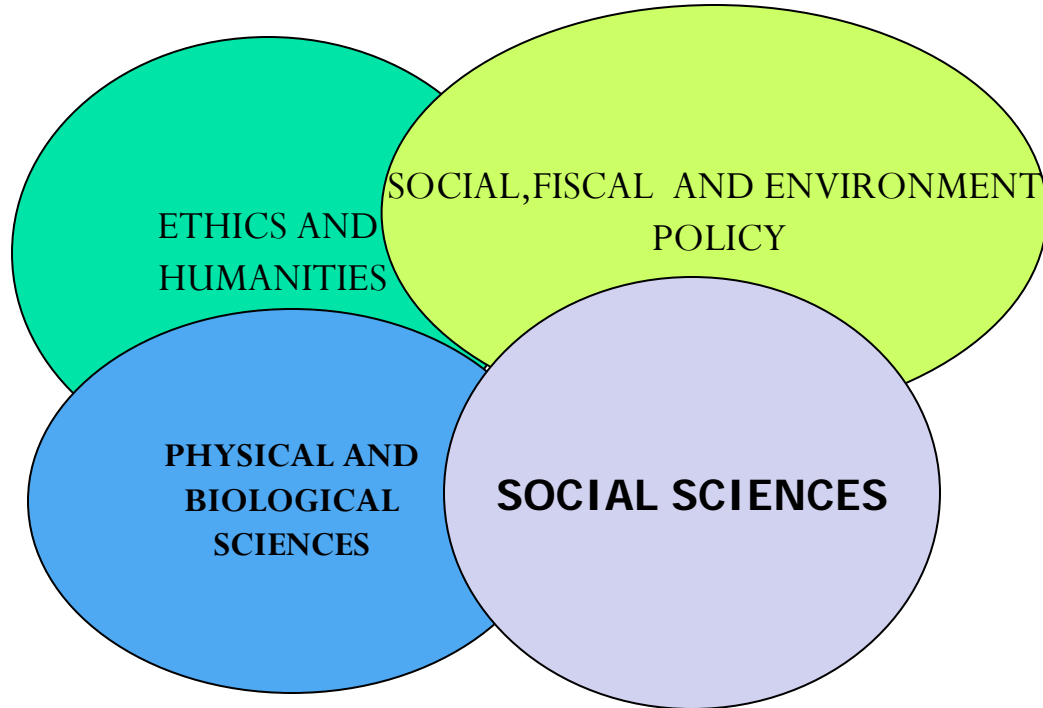
ETHICS AND HUMANITIES

SOCIAL SCIENCES

CONSILIENCE



■ LINKAGES ACROSS DISCIPLINES





Data and Methods What do we want for HTA

- This conference will discuss a number of the issues around the question of data requirements and challenges for the future
- Our National Medicines Policy provides a framework for all the stakeholders involved in HTA- industry, regulators, payers and patients.
- Let's show some leadership and attempt to achieve some consilience. The way of the future of drug development and HTA will be different from the rigid process which has been the paradigm of the past

CONCLUSION



Edward O Wilson

“Consilience. The Unity of Knowledge”

‘The greatest enterprise of the mind has always been and always will be the attempted linkage of the sciences and the humanities.’

‘The ongoing fragmentation of knowledge and the resulting chaos in philosophy are not reflections of the real world but artifacts of scholarship’

‘I think it is inevitable that we will accept the adventure, go there, and find out