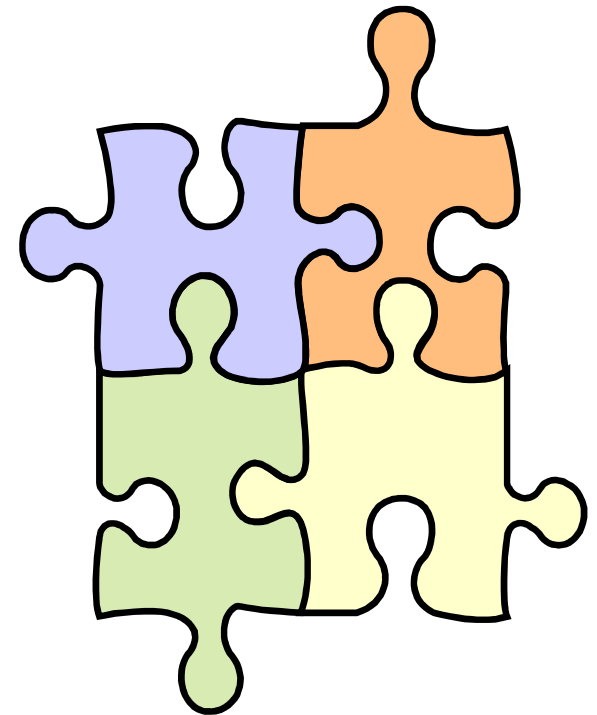


Addressing diversity in CTs

Anita Hardon



That drug is not *hiyang* for him..

- “One week ago I went to the doctor with him, in the provincial hospital. The doctor prescribed Ventolin. I bought it in the pharmacy in town. It cost me 32 pesos. Ventolin is expensive. I gave it to him, but he did not get better. Probably it is not *hiyang* for him. It is hard to find a suitable drug for this small boy”

Not every drug works...for everyone?

- 2003: Dr. Allen Roses, a senior executive of GlaxoSmithKline (GSK), told a scientific meeting in London that the "vast majority of drugs only work in 30 or 50% of people." He cited therapeutic efficacy rates ranging from 25% in oncology to 60% in diabetes and asthma.
- These findings were reported on the front page of the *Independent* newspaper on 8 December 2003. GlaxoSmithKline (GSK), subsequently saw its share price fall last.

GSK " Not every drug will work for everybody. This should come as news to no one. Most people have had the experience of going to the doctor and getting a medicine and having to go back and try another one" (GSK 2004, 51)

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The problem with RCTs

- Mostly for pharmaceutical interventions
- Mostly funded by and conducted for pharma companies
- Conducted for market approval and market expansion/retention.
- Statistical definition of efficacy and safety
- Study populations do not reflect population of users
- Not intended to capture diversity

Hypertension: efficacy and outcome

- Diminished efficacy in black patients, was found for beta-blockers and ACE-inhibitors
- In people aged over 50 years, elevated systolic blood pressure (SBP) is a much more important risk factor for CVD than DBP
- However most past and present RCTs evaluating anti-hypertension medicines have involved short-term efficacy evaluations in younger populations and have used DBP as endpoint.

Regulatory reforms:

1993: NIH Revitalization Act requires the US National Institutes of Health ensure the inclusion of women and also members of racial and ethnic minority groups as participants in every clinical study funded by the agency

“the Director of NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for valid *analysis* of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial”.

EMA

1995-1997: the European Medicines Agency (EMA) adopted guidelines recommending that Phase III trials should be representative of the general population in which the drug is to be used, and that women of reproductive age, children and old people, and ethnic factors should be considered.

Resistance against subgroup analysis

- increases size of trial populations
- Statistical power low
- the cost of trials.

The problem with minorities..

- trial enrolment
- translation
- the validity of (self-reported) measurements in different groups
- compliance and retention

- “...people have more biological similarities than differences. Penicillin will kill bacteria in blacks, whites, Cuban-Americans, Mexican-Americans, men, women, dogs, cats, birds, and petri-dishes” (Piantadosi and Wittes 1993: 565).

Clinical trial subgroup analysis 2000-2004: (Lancet/Jama)

Hypertension (N=17)

Diabetes II (N=10)

By age: 35%

By age: 10%

By ethnicity: 18%

By ethnicity: 0%

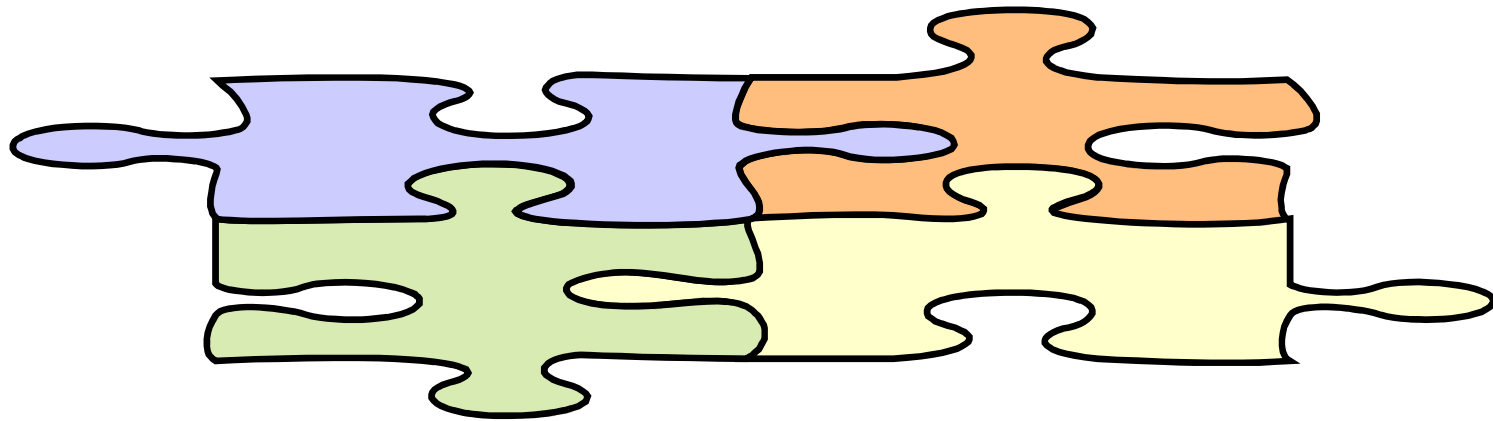
By sex: 35%

By sex: 10%

When subgroup analysis is done: differences dismissed

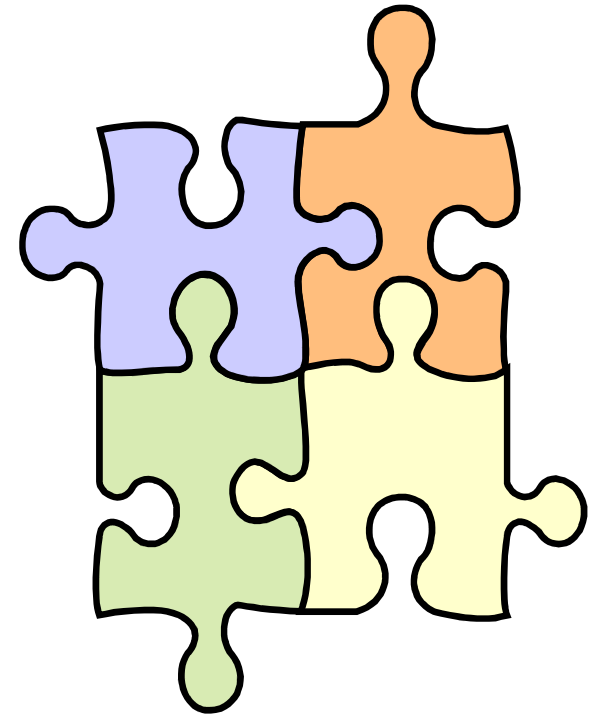
- The RR for prevastatin vs usual care was significantly lower in blacks than non-blacks for CHD events, but was higher for strokes, with no overall difference for combined cardiovascular events ..”.

But what diversity matters?



Dimensions of difference:

- Causes
- prognosis
- Symptoms recognition
- efficacy of interventions
- Co-morbidity
- Concurrent medicine use
- Access
- Experience



Contraceptive pill: diversity in adverse effects

- Risk for thrombosis varies by
- age
- Smoking
- Kind of progestin

Expert meeting ZONmw:

Clinical researchers should take as point of departure that biological (including genetic), social, cultural, economic and environmental factors interact and co-produce efficacy and safety of medicines, and health of individuals. This conceptualisation broadens the diversity research agenda

Underlying problems

- lack of *conceptual* clarity on the kinds of diversity that matter in clinical practice,
- a lack of *agenda setting*, and
- a lack of any *methodological* gold standard on how to address diversity in clinical trials
- Lack of *funding*
- *Very limited Pharma interest* in ‘stratifying’ drug markets

Formulate hypothesis on diversities that matter:

- exploring unexpected phenomena and outliers in trials
- review pharmacodynamic/genetic studies
- consult databases of patients: *explore* effect modification in treatment outcomes,
- Consider also co-morbidities and concurrent medicine use .
- Take adverse drug reaction reports serious: in which populations do the effects occur: why?
- Population based observational studies can be used to explore a wide range of possible associations

Examples

- Studies of health outcomes of drug treatments in Veterans data-base- Libby Roughead
- Studies of reported side-effects of seroxat in emails from the edge, Andrew Herxheimer and Charles Medawar

Test Diversities that Matter

- Focus on specified effect modification
- Define relevant outcome measures
- Define relevant study populations

Research funders should:

- Demand reviews on diversity issues when funding clinical research
- Encourage observational research to identify diversities that matter
- Sustain and expand patient databases and adverse drug reaction reporting to allow for exploration of diversities that matter
- Fund programmatic approaches: from exploration of diversity to RCTs

Regulatory reform?

- Develop mechanisms to encourage pharmaceutical industries to conduct diversity-sensitive clinical trials
- Demand diversity data for market approval

