NEW ZEALAND GUIDELINES GROUP

*Promoting Effective Health and Disability Services*

# Help! We need yours

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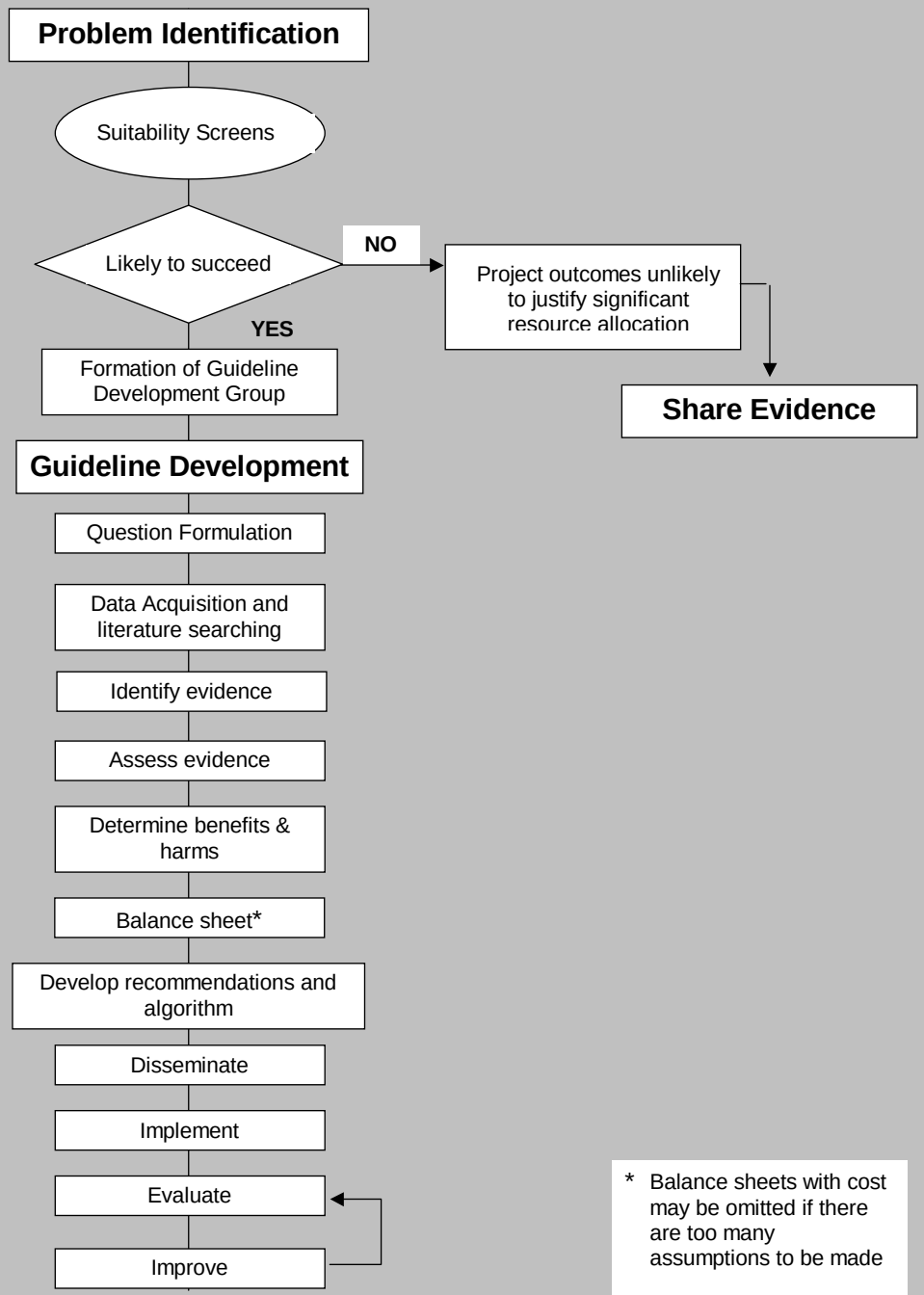
**Driver, project manager and team member of HRT GL**

# Outline of talk

- Process in guideline development
- How well did we do with HRT guideline development?
- Difficulties encountered with group process and subjective judgments about the interpretation of the evidence
- *Evidence based task*

## Fig 1. STEPS IN GUIDELINE DEVELOPMENT




* Balance sheets with cost may be omitted if there are too many assumptions to be made

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# How well did we do? (HRT GL)

- **Suitability screen?**
- Formation of Guideline Development Group?
- Conflicts of interest?
- Scope of GL and clinical questions?
- Searching?
- Data extraction/evidence tables?
- Appraisal and grading?
- Considered judgment/group process?
- Consensus/minority opinion?

# Suitability screen

- Clear evidence of variation in prescribing of HRT throughout NZ
- Increase in HRT prescriptions over the previous decade
- HRT prescribed for symptoms that were not necessarily associated with the menopause

*CLEAR NEED FOR A GUIDELINE ON APPROPRIATE PRESCRIBING OF HRT*

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# Formation of Guideline Development Group-the multidisciplinary team

The guideline development group require wide representation including expertise in guideline development,facilitation and mediation,clinical expertise(about the area being considered),primary care representation,consumer and cultural representation.

Report prepared by the Wellington SOM for NZGG (2001)

# Multidisciplinary Team (1)

- Executive Director of womens group (consumer)
- Prof Nursing
- Prof Reproductive Medicine
- Prof Epidemiology
- Prof Medicine and Endocrinology
- Cardiologist
- 2 reps from Effective Practice Institute
- Reproductive Endocrinologist
- 3 GPs (one Maori and one PI)
- Senior Lecturer Women's Health (n=13)

# Multicisciplinary Team (2)

*Sufficiently multidisciplinary?*

- Both Maori and PI reps were GPs – what about consumer representation for these ethnic groups?
- More consumers? Eg. A "consumer" of HRT?
- More women's health experts?
- Anyone else missing?

# Multidisciplinary Team

- Each member should represent a constituency
- HRT members selected arbitrarily – colleagues and friends
- All disciplines represented eg. Cardiologists, endocrinologists, consumer etc.
- Members did not report back to their group
- 3 drivers chosen (women's health expert, consumer and cardiologist)

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# Conflicts of interest

- Should be declared at the beginning of the process
- Relationships with pharmaceutical companies?
- Or also personal inherent philosophical beliefs regarding the topic?
- HRT is good or bad?

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# Scope of GL and clinical questions?

- GL topic was not in the usual format i.e. *management of X* (named condition)
- HRT used for a huge number of indications – in some cases women did not know why they were on HRT
- No questions - instead evidence sought on the "indications" for HRT e.g. heart disease,breast cancer,effect on bone density etc.

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# Searching

- Guideline divided into sections (based on indications) – eg. Cardiac disease, Bone, Skin, Libido etc.
- Members from the group (experts) took on responsibility for writing these chapters and undertaking searching
- Independent searching for most topics – searching expert
- The most rigorous evidence included: RCTs and systematic reviews if possible

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# Data extraction/evidence tables?

- Searches identified a very large number of studies
- No resources to extract data and summarise all of the studies in evidence tables
- Writing of text by experts based on the retrieved evidence

*POSSIBILITY OF BIAS THROUGH SELECTIVE INCLUSION OF STUDIES THAT CONFIRMED EXPERT OPINION*

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# Appraisal and Grading?

- SIGN grading system used – 2 levels:
  - individual studies
  - body of evidence
- No resources for training guideline writers in the system
- May have been applied inappropriately – no independent verification except for a small sample

*Figure 6.2: SIGN grading system*

***Levels of evidence***

| | |
|---|---|
| 1++ | High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| 1+ | Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| 1 - | Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias |
| 2++ | High quality systematic reviews of case-control or cohort studies<br>High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal |
| 2+ | Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal |
| 2 - | Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal |
| 3 | Non-analytic studies, e.g. case reports, case series |
| 4 | Expert opinion |

***Grades of recommendation***

| | |
|---|---|
| **A** | At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or<br>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<br>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<br>Extrapolated evidence from studies rated as 2++ |
| **D** | Evidence level 3 or 4; or<br>Extrapolated evidence from studies rated as 2+ |

***Good practice points***

✔ Recommended best practice based on the clinical experience of the guideline development group

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# Considered judgment/group process?

- Guideline developers must make a considered judgement about the **generalisability, applicability**, **consistency**, and **clinical impact** of the evidence to create a clear link between the evidence and recommendation

Harbour R

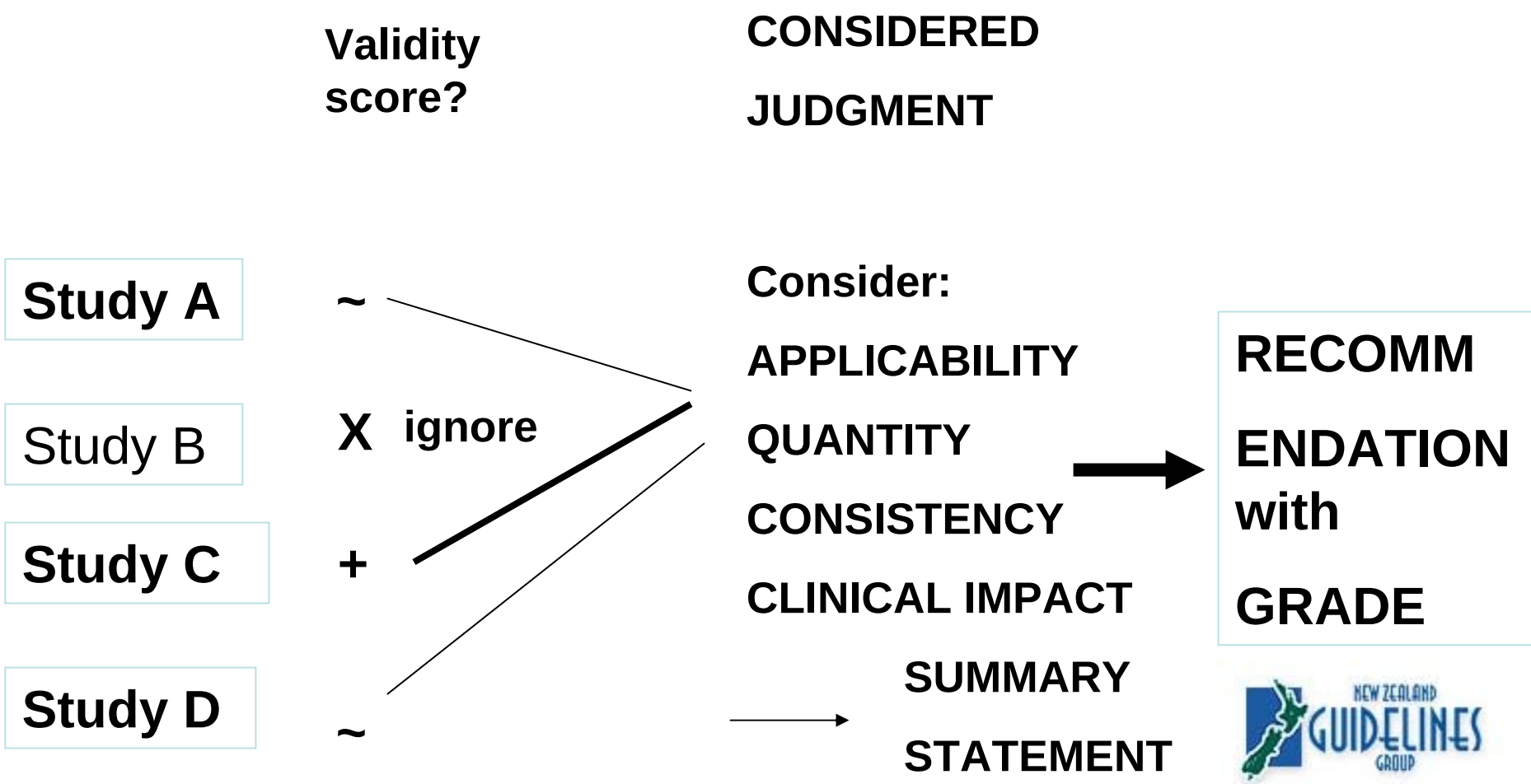
BMJ 2001;323:334-6

# Considered judgment form

*Key question* *Evidence table ref*

- **Volume** of evidence
- **Consistency** of evidence
- **Applicability** of evidence
- **Clinical impact** of evidence
- **Evidence Summary**
- **Recommendation** with grade (associated with the strength – not direction – of the evidence)

# From evidence to recommendations



# Considered Judgment

Having completed a rigorous and objective synthesis of the evidence base, the guideline development group must then make what is essentially a **subjective judgment** on the recommendations - one that can validly be made based on clinical experience as well as knowledge of the evidence...

# Considered Judgment

Increasing the role of subjective judgement risks the reintroduction of bias into the process. It must be emphasised that this is not the judgment of an individual but of a carefully composed multidisciplinary group – thus this process should minimise bias.

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# First steps - Establishing the process

GRADE Working Group -

- prioritizing problems
- selecting a panel
- declaring conflicts of interest
- agreeing on a group process

# Considered judgment/group process

- No Considered Judgment process used to reach consensus
- Chapters of guideline submitted and sent to whole group for “approval”
- Graded recommendations based on the evidence written by chapter writers
- No process to handle disagreements

# Consensus

- A major difficulty was the publication of new evidence that changed original recommendations e.g. WHI
- New publications continued to be released over the next 2 years requiring re-visiting of the recommendations
- Goodwill of the group severely compromised
- EMAIL fatigue! - small group meetings with drivers
- Larger group disagreement
- Members unwilling to register minority opinions – extreme difficulty in reaching consensus

# Group Process - consensus

- Group decision making is always required in GL development
- Each guideline development team (GDT) needs to select a method for managing group decision making – whether it is informal e.g. show of hands or a formal method
- There should be a transparent method for managing "dissent" or minority opinion – e.g. recorded in the GL somewhere
- Methods to manage the group process particularly important where the GL topic is controversial

# Report prepared by the Wellington SOM for NZGG (2001)

Guideline development teams undertake a complex task. They are (often) learning the development process, resolving concerns within the development group, representing a clinical or consumer interest as well as maintaining their everyday professional role.

# Issues in interpretation of the evidence – HRT GL

Between August 2003 and January 2004 the journal Human Reproduction ran a series of 6 articles

"Issues to debate on the WHI study"

# Issues to debate on WHI

HRT: an epidemiological dilemma?

This review of both studies (HERS and WHI) will show the methodological weaknesses….and the reasons for limited generalizability of the ….results

Machens K(R+DSchering) et al

# Issues to debate on WHI

Epidemiological or randomised clinical trials - time out for HRT studies?

The HRT part of WHI was performed as a double-blind placebo-controlled design. However, the fact that only 18,845 women provided consent for randomisation, out of the 373,092 women ..... certainly points to *bias due to selection of the study population*

Anette Tonnes Pedersen and Bent Ottesen

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# Issues to debate on WHI

HRT and acute coronary outcomes: methodological issues between randomised and observational studies

Despite randomization, the reported small increase in risk in the WHI study could be spurious because of *differential unblinding of HRT users*, which could have resulted in higher detection rates of otherwise clinically unrecognised myocardial infarction in these women.

E.Garbe and S.Suissa

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# And Again

- In WHI, 44.4% of women on active RV 6.8% of placebo had Rx *unblinded* (due to vaginal bleeding)
- Among these, *detection bias* could not be excluded
- In terms of awareness of exposure status it came to resemble an *observational study*
- For differences in order of 0.7-0.8/1000 per year, it is not possible to discriminate between *causation and detection bias.*

Shapiro S,Dept Epidemiology,Columbia University.Climacteric 2008

# Followed By

*Editor's comment:*

Dr Shapiro's paper was reviewed favorably by other reviewers - we welcome submission of other comments.

# Comment

- Reanalysis excluding unblinded participants would be of interest
- I do not however believe it is ethical to wait for such data before accepting the need to adjust the current use of this Rx
- The fact remains that in US 1.7 million women on long term Rx for health maintenance - 2000
- An extra 1370 breast cancers,1200 CHD,1370 strokes,1370 PE per year

Tucker G, Health Statistics Unit ,Govt Sth Australia

# More Comment

WHI - Underpowered for CHD events

- could not have detected cardioprotective effects when started in early menopause
- Manson – nonstatistically significant decrease risk CHD in women < 10 years from menopause
- If study sufficiently powered this might have achieved significance

Naftolin F. Fert Steril 2004

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# European Medicines Evaluation Agency

- Risk/benefit balance of HRT does not justify use as first line Rx for prevention of osteoporosis

- Dr. David Purdie resigned from CSM in UK as consequence of similar advice

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# PREMPRO LAWSUITS

## Get Legal Help Here

Prempro Lawsuits. A national study of hormone replacement therapy by the Women's Health Initiative concluded that women taking Hormone Replacements are at increased risk of breast cancer, coronary heart disease, stroke and pulmonary embolism.

Hormone Replacement Therapy is used by millions of women and these adverse effects can harm substantial numbers of women. It is the responsibility of the drug manufacturers to protect women from harm resulting from use of their products.

If you or a loved one has suffered harm as a result of Prempro hormone replacement therapy, contact us to discuss your legal options.

Get Legal Help

Hormone Replacement Therapy

Women's Health Initiative Study

PREMPRO Dangerous Side Effects

Potential Lawsuits

# Head of German medicines body likens HRT to thalidomide

Jane Burgermeister *Vienna*

Doctors in Germany should drastically reduce the amount of hormone replacement therapy (HRT) that they prescribe to older women, a key commission has recommended.

Issuing its first guidelines on HRT to doctors in Germany, the country's Commission on the Safety of Medicines said that new international studies had shown that the risks of HRT clearly outweighed the benefits.

It recommended that doctors offer the treatment only to

and international tragedy." Comparing it to thalidomide, a drug that caused thousands of babies to be born with birth defects in the 1950s, he said that the "naive and careless use of a medication that is perceived as natural and optimal" had caused many unnecessary deaths among women.

Professor Eberhard Greiser, of the Institute for Prevention Research in Bremen, said in an interview with the state health insurance press service that the


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# And Finally

The most amazing event of the past 2 years has been the emotional polarization of postmenopausal hormone therapy

Leon Speroff. Maturitas 2004