

# Prophylactic platelets; General introduction and Changing practice

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# My job

This talk:

- Introduction
- Prophylactic platelets
- Changing practice

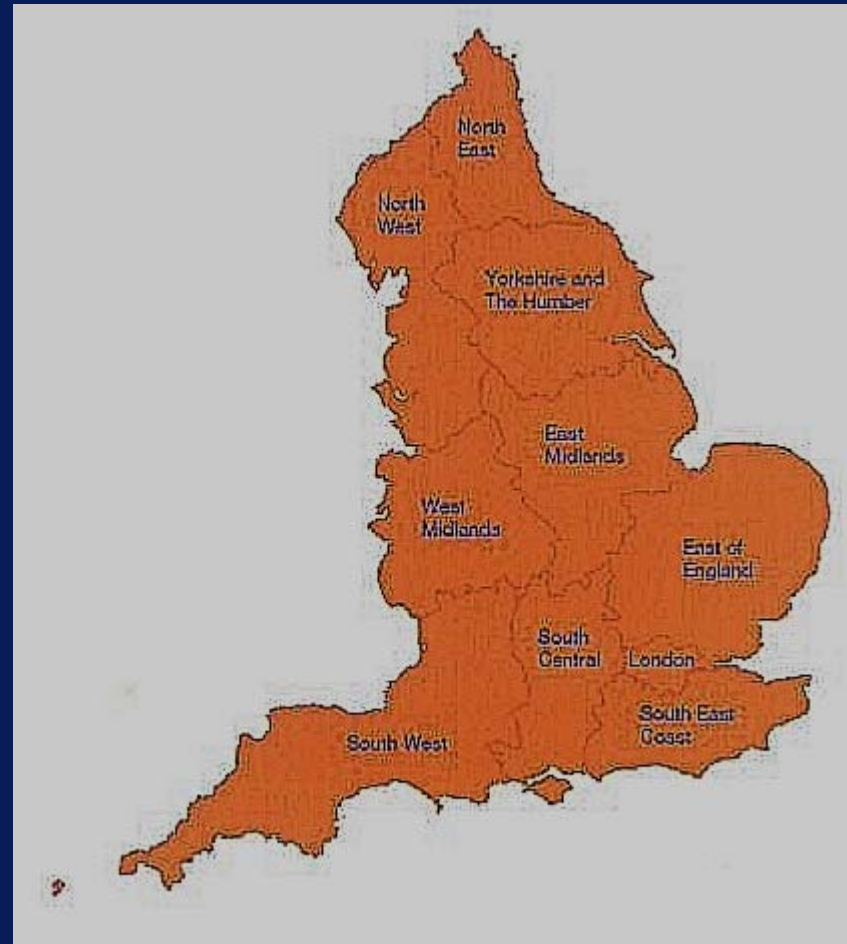
Joint position as Consultant Haematologist:

- Hospital liaison - local hospital and regionally
- National – clinical research
- Clinical – paediatric haematology

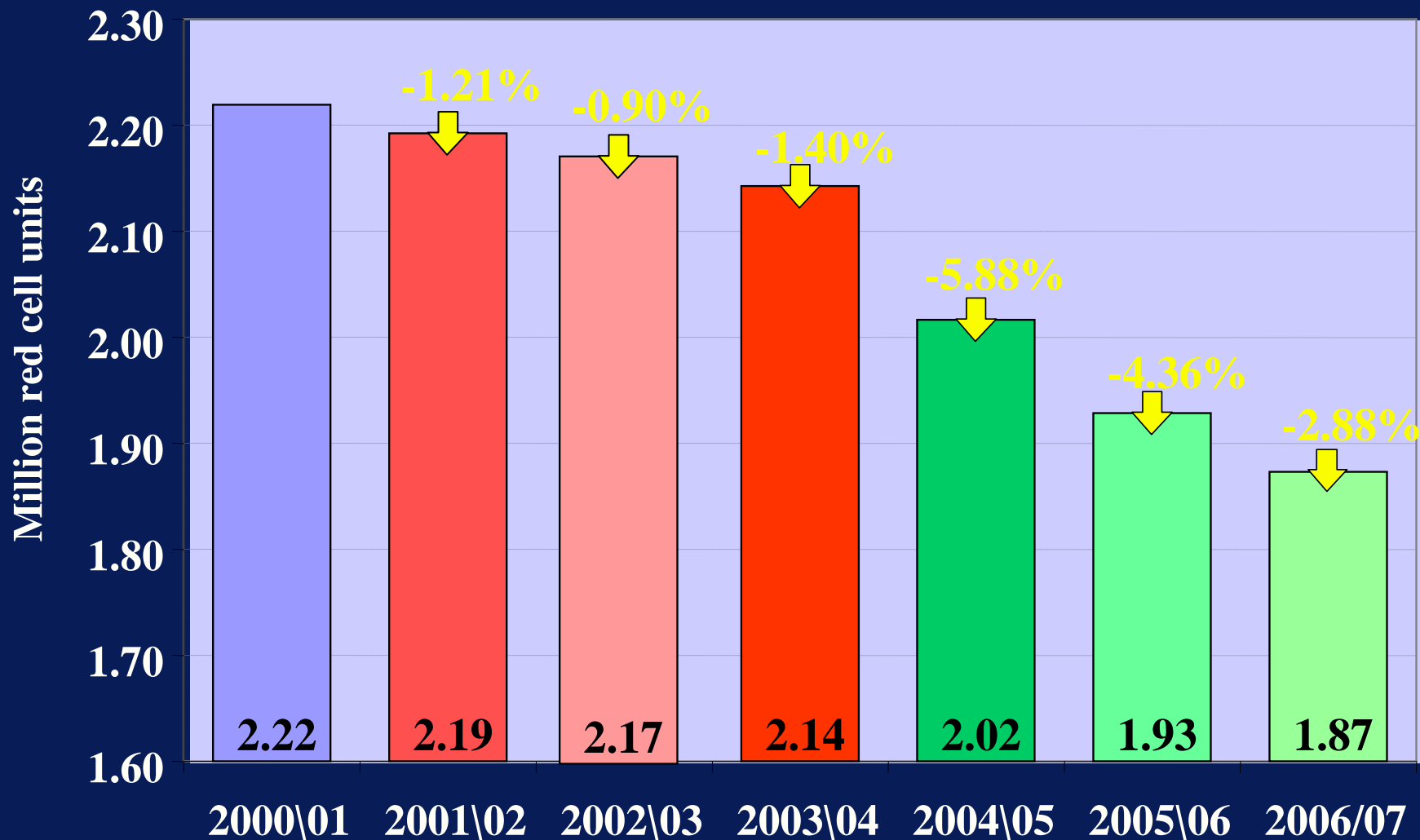
# Better Blood Transfusion Initiatives: National programme of action for the NHS

- Regional and Hospital Transfusion Teams
- Ensure Better Blood Transfusion is an integral part of NHS care
- As part of clinical governance, make transfusion safer (daunting agenda of training/audit/guidelines)
- Avoid unnecessary use of blood
- Provide better information to patients and the public about blood transfusion

# England – regional structures for ‘PCT’



# Outcomes: Red Cell Demand in Eng & N Wales



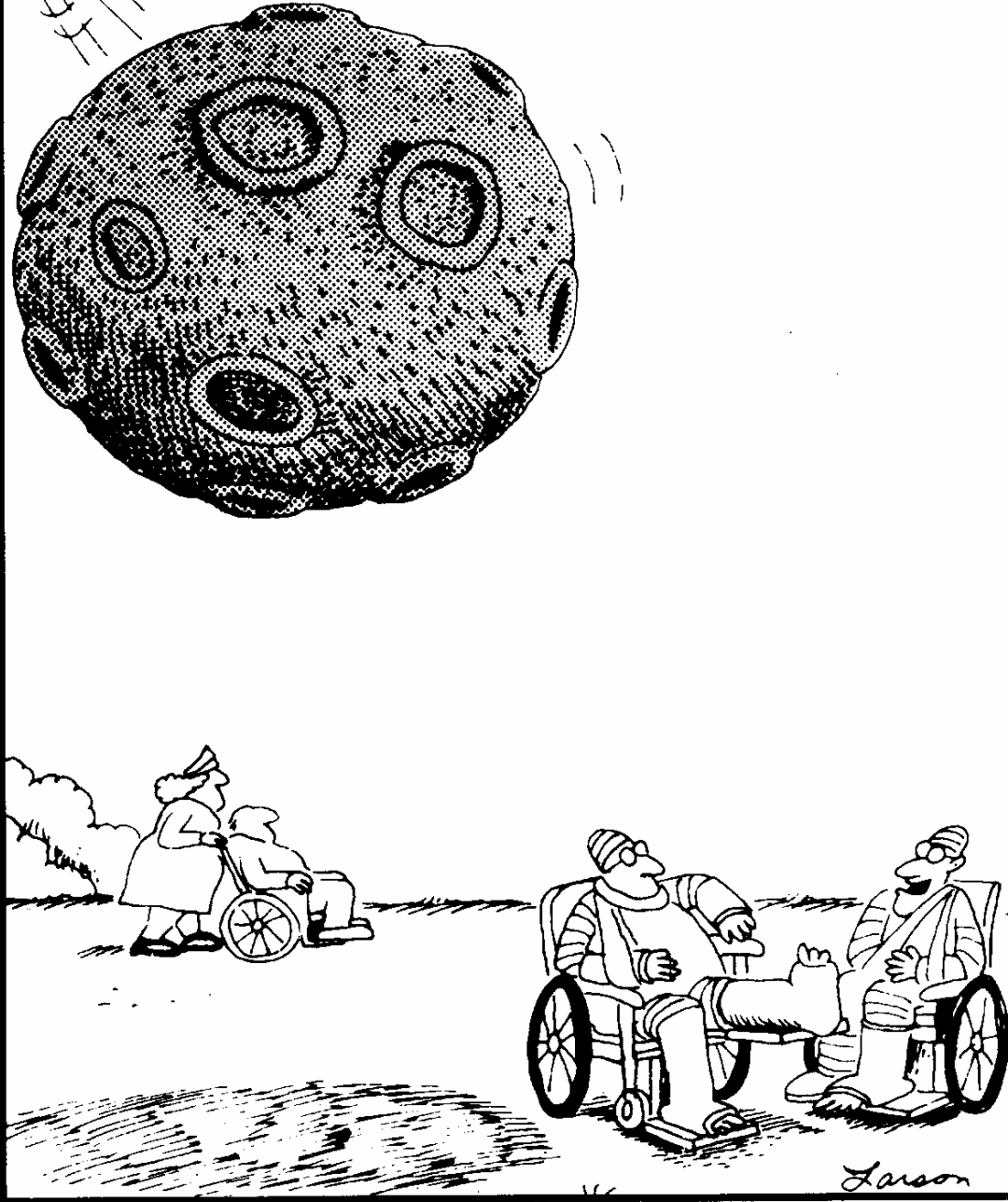
# Will my transfusion do more good than harm?

## Patient/Public:

Anxiety about the risks of transfusion, largely generated by HIV and vCJD

## PCT Clinicians:

1. Variability in practice;
2. Uncertain *evidence-base* for efficacy of appropriate transfusion,



**“You’re kidding! ... I was struck twice by lightning too!”**

# 1. Variability - UK comparative audits:

## Transfusion in acute upper gastrointestinal bleeding

257 UK hospitals invited



217 hospitals (84%)

8939 cases submitted



1090 insufficient data

1099 not UGIB

**6750** analysed (76%) – Peptic U, varices



# Practice against standards

**6750 analysed**

**2922 (43%) RBC**

**3828 (57%) no**

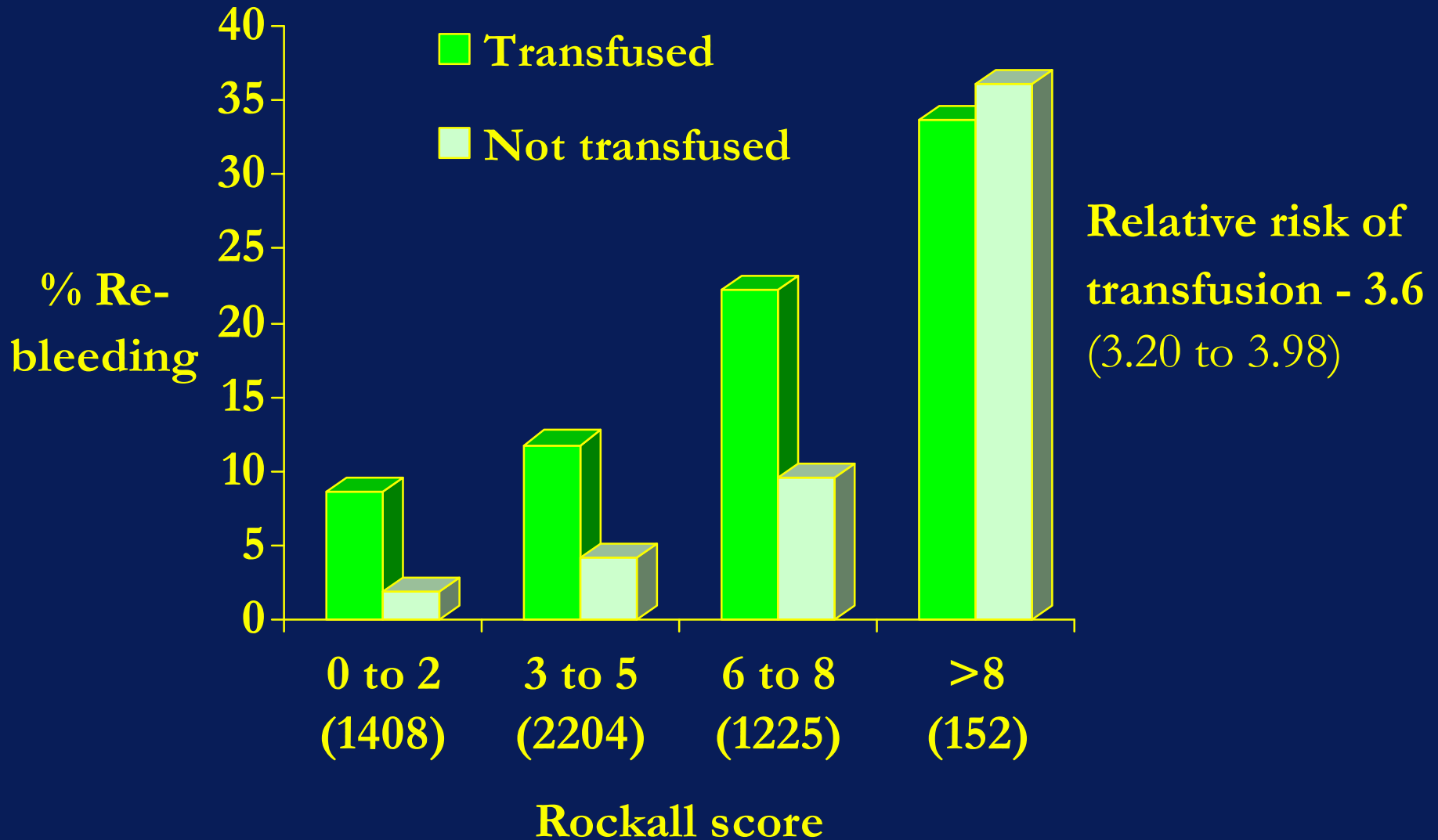
**77% of these in first 12 hours**

**15% of these *not* indicated**

**10% normal Hb and stable**

**<5% no Hb**

# RBC transfusion in first 12 hrs and re-bleeding



Re-bleeding and mortality rates higher in transfused patients

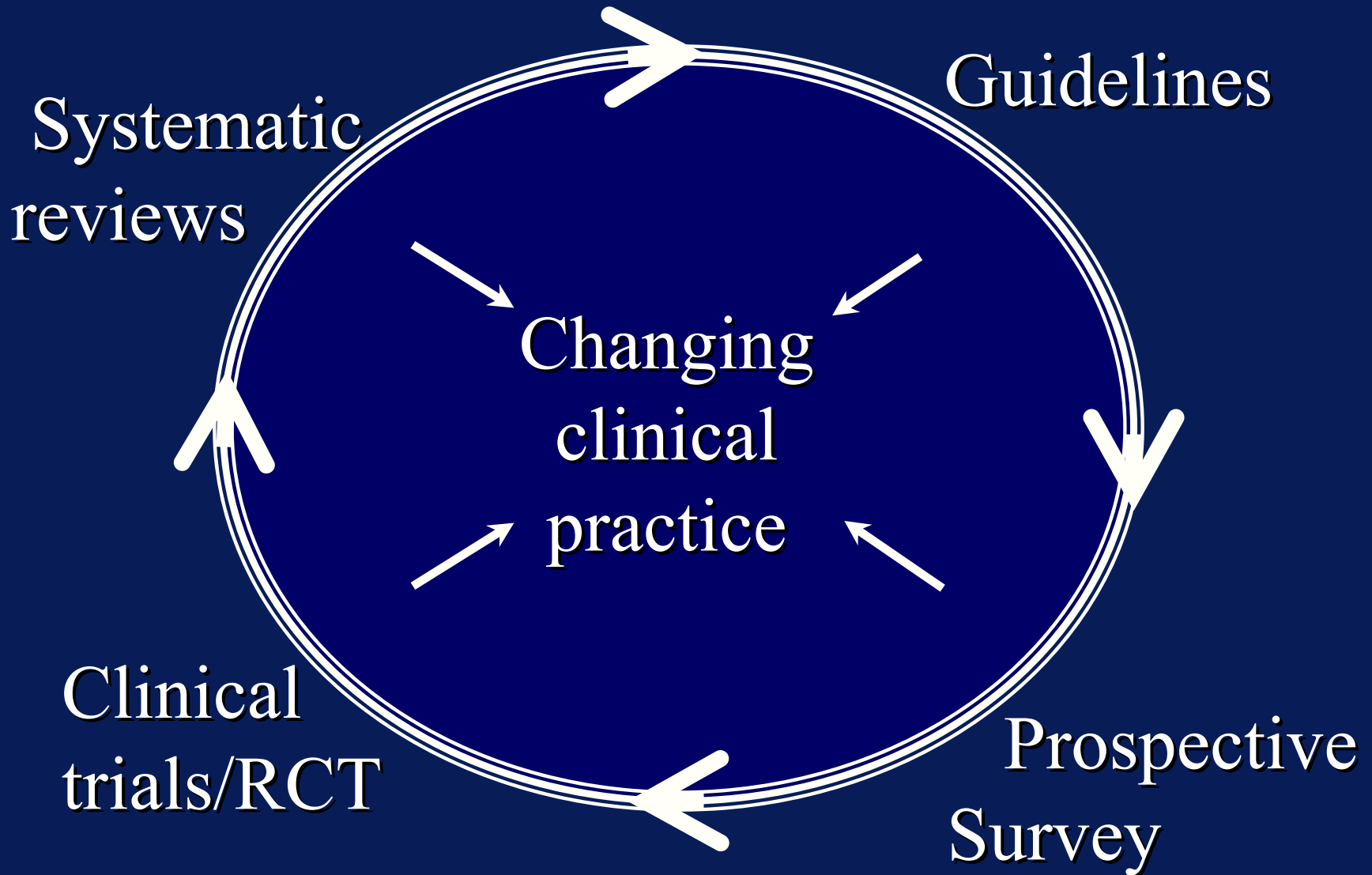
# Hypothesis generating: RBC transfusion and re-bleeding

One RCT - 50 patients with non-variceal UGI bleeding

|             | RBC transfusion first 24hrs; N=24 | No transfusion first 24hours N=26 |
|-------------|-----------------------------------|-----------------------------------|
| Re-bleeding | 9                                 | 1                                 |
| Deaths      | 2                                 | 0                                 |

*Blair S et al. Br J Surg 1986; 73: 783-85*

## 2. Uncertain Evidence Cycle



# Definitions – systematic review

Systematic review process:

- » focused question
- » multi-authorship/different backgrounds
- » being transparent to ↓ bias
- » explicit methods for inclusions/exclusions
- » appraising studies - quality
- » effect sizes & graphical display to compare

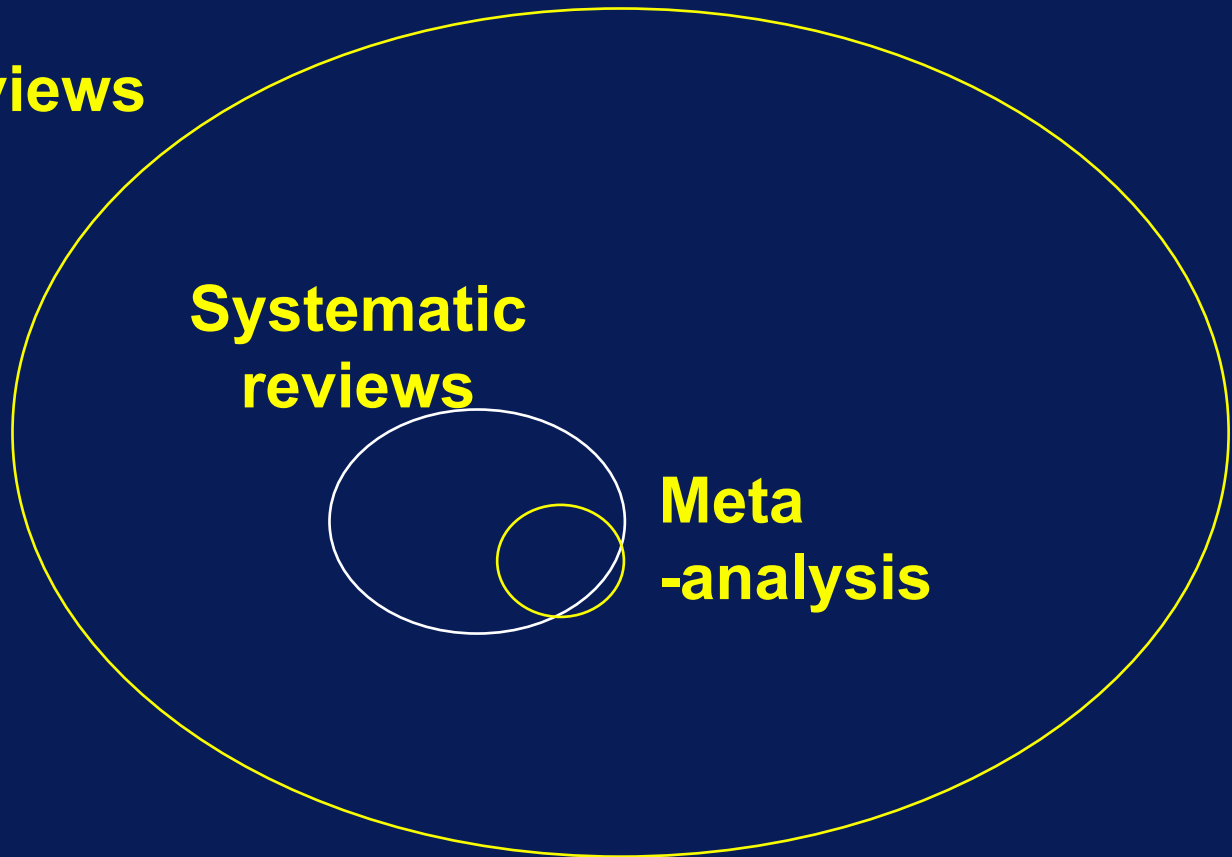
e.g. Cochrane Collaboration

# Reviews - Qualitative and Quantitative (meta-analysis): examples in transfusion

**All reviews**

**Systematic reviews**

**Meta-analysis**



# How systematic reviews relate to new RCT

## Clinical study or trial

- » unit of observation is the individual patient
- » in primary research new data is collected
- » intent-to-treat analysis

## Systematic review

- » unit of observation is the study:
- » i.e. the measured effect for an intervention
- » need data from all trials to contrast

# NBS core commitment to clinical research

- **Systematic Reviews Initiative (SRI)**

Reviews

Understanding and changing practice

- **Clinical Studies Unit (MRC CTU)**

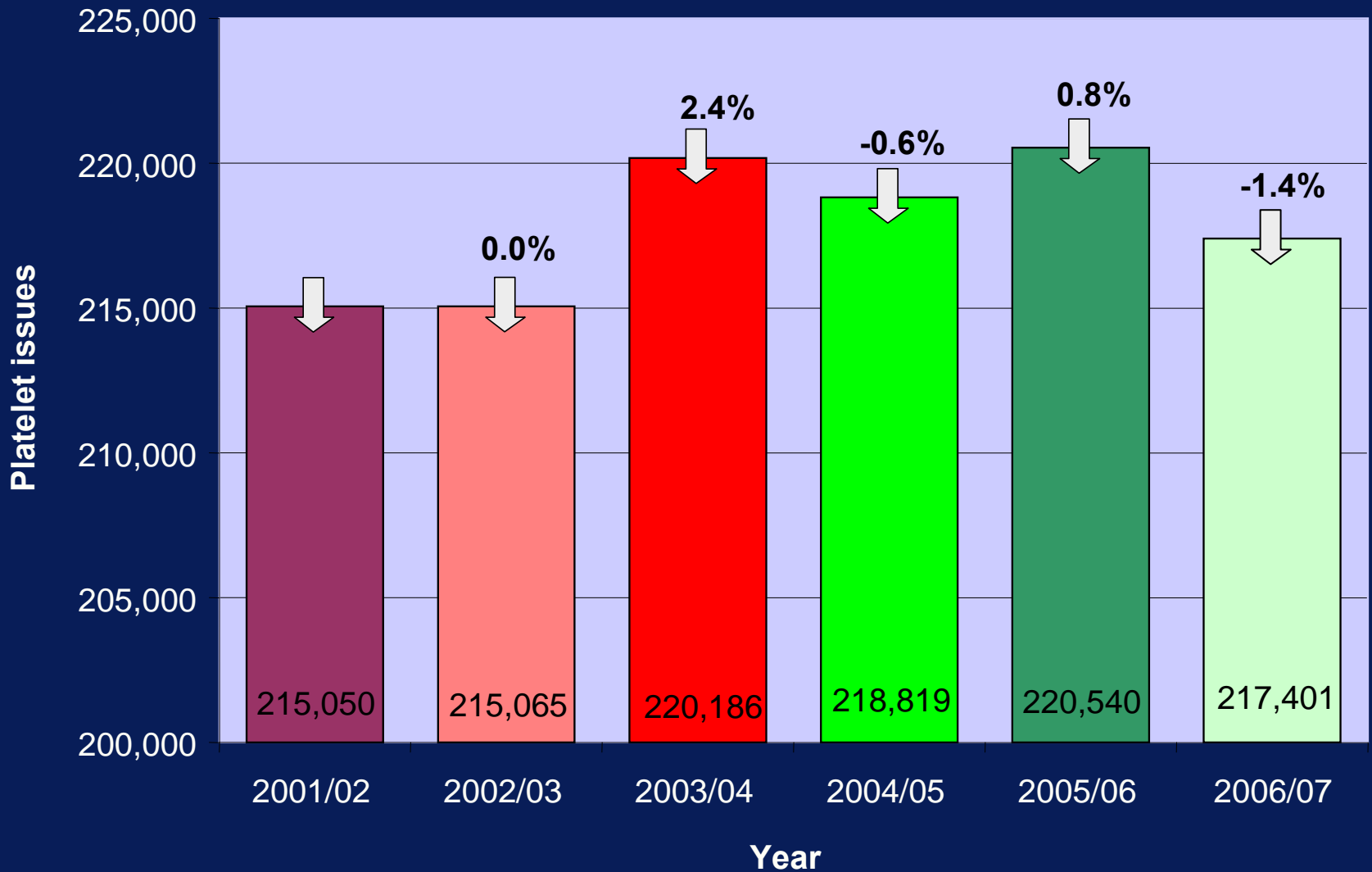
Epidemiology

Product

Observational (prospective) surveys

Full RCTs

# Platelets: Demand 2001 – 2007



# Platelet transfusion: key issues

- **Product type**
- **Dose**
- **Clinical use**

# Platelet transfusion: product type

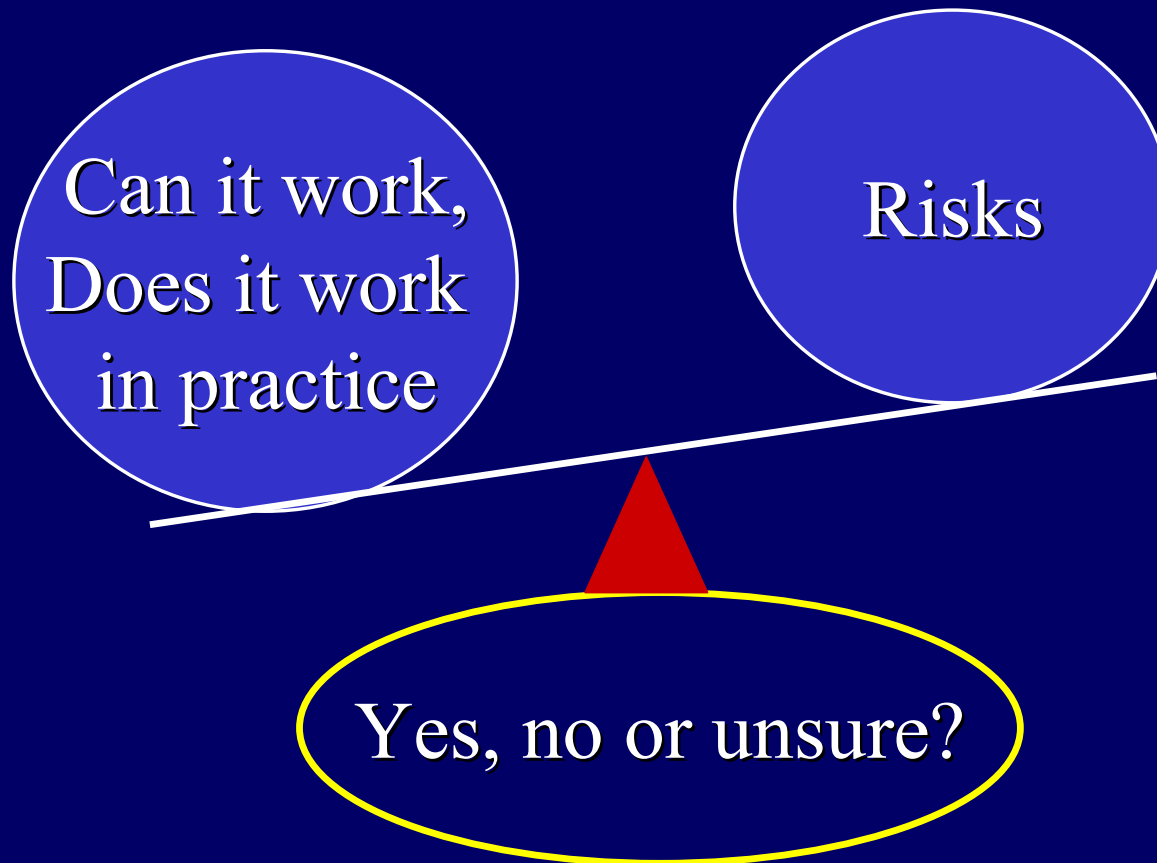
- Many different types of platelet products
- Systematic review completed but not yet published (Dumont & Heddle)
- Main finding: superior platelet increment, recovery and survival with apheresis v whole blood platelets
- But clinical significance of these findings are unknown

# Haematology patients - Revised current BCSH guidelines for clinical use

- Therapeutically
- As prophylaxis, threshold of  $10 \times 10^9/L$  as safe as higher levels for patients without risk factors such as sepsis, and coagulopathies

**BCSH. Br J Haematol, 2003, 122, 10-23.**

# Clinical use of platelets - presumed benefits & finite risk?



Good understanding of many of the risks - haemovigilance

# Adverse consequences - Thrombopoietin

- TPO is adsorbed through its ligand onto surface of transfused platelets
- By avoiding additional platelet transfusions, TPO levels may rise further & sooner
- Association between ↓ numbers of transfused platelets, ↑ plt production as soon as megas appear, and ↓ duration of thrombocytopenia

# Issues for use of platelet transfusion

1. Prophylaxis versus no prophylaxis
2. What is the correct dose of platelets, and how often should they be given?
3. What should be the 'trigger' for prescribing prophylactic platelets in haem-onc patients?

# ASH 2007, Sherrill Slichter

“Are prophylactic platelet transfusions necessary: has not yet been resolved”

“A therapeutic strategy to transfuse platelets only with the onset of active bleeding has been documented to be safe in a select group of patients (in one recent study)”

# Platelet transfusion: dose

- No consensus on optimal platelet dose for prophylactic transfusions
- ‘Low dose’ - reduced donor exposure, costs, and duration of thrombocytopenia?
- ‘High dose’ – reduced morbidity and mortality due to bleeding, longer transfusion-free interval, and reduced overall platelet requirements?

# What Platelet Dose? - clinical trials

| Author   | Dose x 10 <sup>11</sup> |
|----------|-------------------------|
| Roy      | ?Low vs Standard        |
| Tinmouth | Low vs Standard         |
| Sensebe  | Standard vs High        |
| Norol    | Standard vs High        |
| Klumpp   | Standard vs High        |

# Platelet transfusion: dose

Cid & Lozano. Transfusion 2007, 47, 464-470

- In 4/5 trials, there was a significant increase in the post-transfusion platelet increment in the high dose compared to the low dose group,
- 3/5 trials assessed bleeding as an outcome measure, but none detected a significant difference between the groups receiving high and low dose platelets
- Overall conclusion - further trials are needed to define optimal dose of prophylactic transfusions

# Tinmouth et al, Transfusion 2004; 44:1711

- One RCT - low vs standard dose plts in haem-onc prophylaxis (n=111)
- Major bleeding:
  - » low dose = 10.7% (5.1-21.2)\*
  - » standard dose = 7.3% (2.9-17.2)
- \*2 extra events when plts >100.
- More minor bleeds in standard dose group
- 25% fewer plt units used

# Severe Bleeding Events

- Evidence that severe bleeding events occur at a wide range of platelet counts from surveys and RCTs
- Including levels which would not trigger platelet transfusions
- Multi-factorial nature of severe/intracranial bleeds

# Current trials of dose

- NHLBI – 3 arms (low vs standard vs high), sample size 450/arm (1350 total)

Completed – awaiting analysis

- BEST (SToP) – 2 arms (low vs standard)

Closed

## 2. What should be the 'trigger' for prophylactic platelets in haem-onc?

### Four randomised trials

- Contemporary
- 2 trials AML, 2 trial BMT
- Numbers randomised range 78-255
- 3 compared triggers 10 and 20 x 10<sup>9</sup>/L

# Rebulla et al. NEJM 1997;337:1870: RCT in AML

| Threshold:                    | $10 \times 10^9/L^*$ | $20 \times 10^9/L$ |
|-------------------------------|----------------------|--------------------|
| Number                        | 135                  | 120                |
| Major bleeding episodes       | 21.5%                | 20%                |
| 1                             | 15.6%                | 15.0%              |
| 2-4                           | 5.9%                 | 5.0%               |
| >4                            | 0                    | 0                  |
| Days with major bleeding      | 3.1                  | 2.0                |
| Hemorrhagic deaths (cerebral) | 1**                  | 0                  |



**21.5% fewer transfusions**

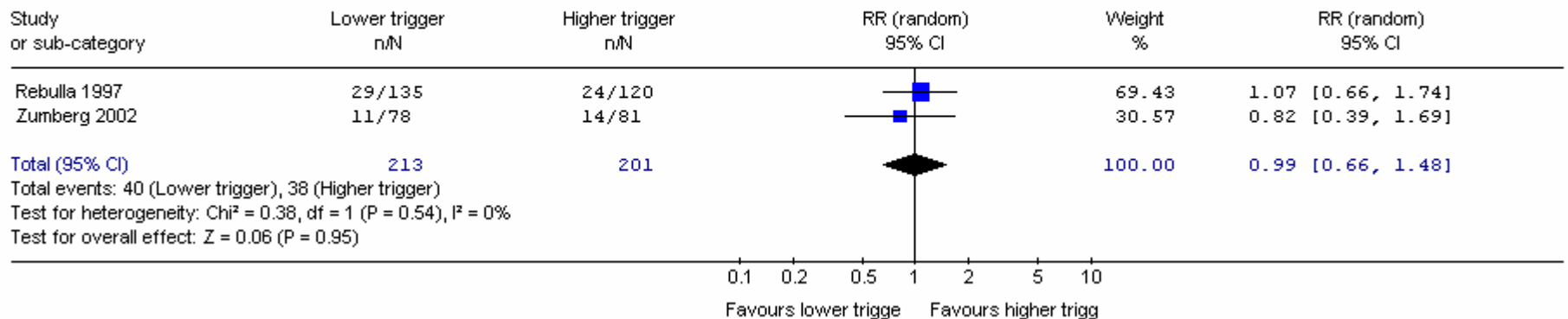
\*or  $10-20 \times 10^9/L$  for temp  $38.0^\circ C$ , prior invasive procedure etc;

\*\* plt =  $32 \times 10^9/L$

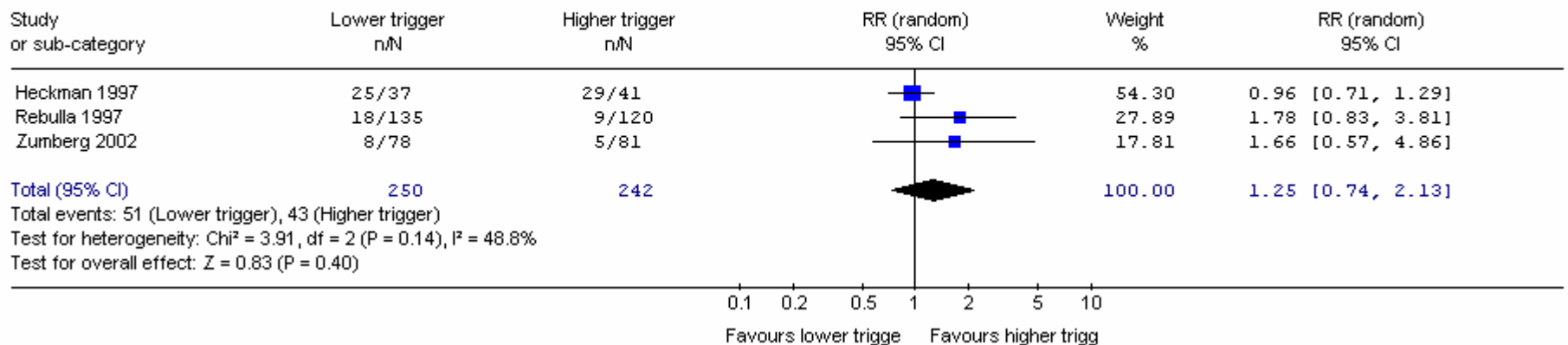
**NB variable compliance with triggers, for a number of reasons including risk factors & violations (28%)**

# Major bleeding events & mortality

Review: Prophylactic platelet transfusion for haemorrhage after chemotherapy and stem cell transplantation  
 Comparison: 02 Prophylactic platelet transfusion at one trigger level versus another trigger level  
 Outcome: 04 Numbers of participants with major or more severe bleeding events

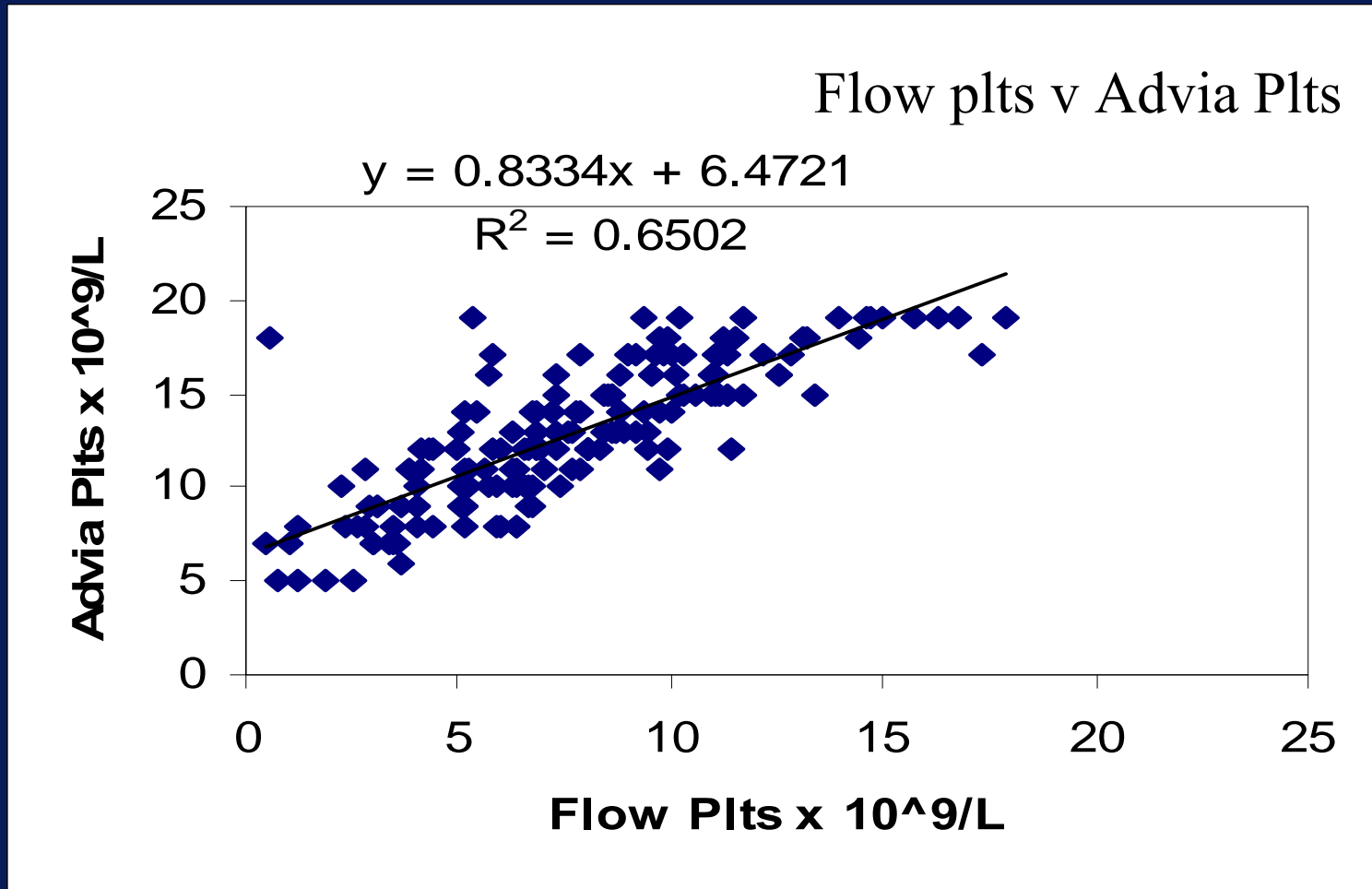


Review: Prophylactic platelet transfusion for haemorrhage after chemotherapy and stem cell transplantation  
 Comparison: 02 Prophylactic platelet transfusion at one trigger level versus another trigger level  
 Outcome: 01 Mortality from all causes



Do the studies, even combined, have adequate power for equivalence

# Other issues - Threshold counts across groups, reliability of low counts, reticulated plts



### 3. Is rationale for prophylactic platelet transfusions based on rigorous studies

- Is prophylaxis effective?
- What is the risk-benefit balance?

# Relationship between platelet count and bleeding

- *Gaydos et al 1962, NEJM*: manual counting ( $<1-5 \times 10^9/l$ ) and bleeding signs
- Relationship but no threshold effect
- Intracranial haemorrhage
  - refractory leukaemia
- Aspirin, Quality control, Supportive care

# RCT: Prophylactic v therapeutic

- 3 smaller randomised trials
- Trials published 1978-1982
- Significant heterogeneity in outcomes
- 2 trials AML, 1 trial ALL in children
- Age of studies
- Total numbers randomised ranged 21-56
  - » Studies underpowered & little confidence

# Platelet counts, transfusions & bleeding

## John Hopkins Oncology Centre

- 1988 - 1997, records of bleeding outcomes
- Retrospective review of 79546 thrombocytopenic days in 2942 patients
- No relationship between morning or lowest daily platelet count and bleeding
- Multivariate analysis (uraemia, hypoalbuminaemia, recent previous bleed)  
ie patient specific factors

# Local audit: Lack association between platelet count & bleeding on 292 days observation

| % Days      | 1-10 | 11-20 | 20-50 |
|-------------|------|-------|-------|
| No bleeding | 51   | 52    | 51    |
| WHO Grade I | 39   | 33    | 38    |
| WHO Grade 2 | 10   | 15    | 12    |

OR bleeds WHO Gd II = 0.86 (95%CI 0.22- 3.33) for counts <10

# 1. Difficulties of defining and grading bleeding events; &

## 2. are we aiming to prevent all bleeds?

### Grade 1

- Mild/moderate petechiae, purpura,
- Mild/moderate oropharyngeal bleeding, epistaxis <30 minutes in duration

### Grade 2

- Melaena, haematemesis, haemoptysis, fresh blood in stool, musculoskeletal bleeding or soft tissue bleeding **not requiring red cell transfusion within 24 hours of onset and without haemodynamic instability**
- Profuse epistaxis or oropharyngeal bleeding i.e. > 30 minutes in continuous duration
- Symptomatic oral blood blisters i.e. bleeding or causing discomfort
- Extensive petechiae, purpura i.e. numerous in number and/or positioned on either face or abdomen and/or spreading by comparison to previous assessment
- Visible blood in urine
- Bleeding from invasive sites requiring 2 or more dressing changes in a 24hr period because it has become saturated with blood
- Unexpected vaginal bleeding saturating 2 or more pads with blood in a 24hr period
- Red cells in body cavity fluids obvious macroscopically

### Grade 3

- Melaena, haematemesis, haemoptysis, haematuria -including intermittent gross bleeding without clots, abnormal vaginal bleeding, fresh blood in stool, epistaxis, and oropharyngeal bleeding, bleeding from invasive sites, musculoskeletal bleeding, or soft tissue bleeding **requiring red cell transfusion specifically for support of bleeding within 24 hours of onset and without haemodynamic instability**
- Body cavity fluids reported as grossly bloody in laboratory, nursing, or medical case notes
- CNS bleeding noted on CT (computerised tomography) without clinical consequences

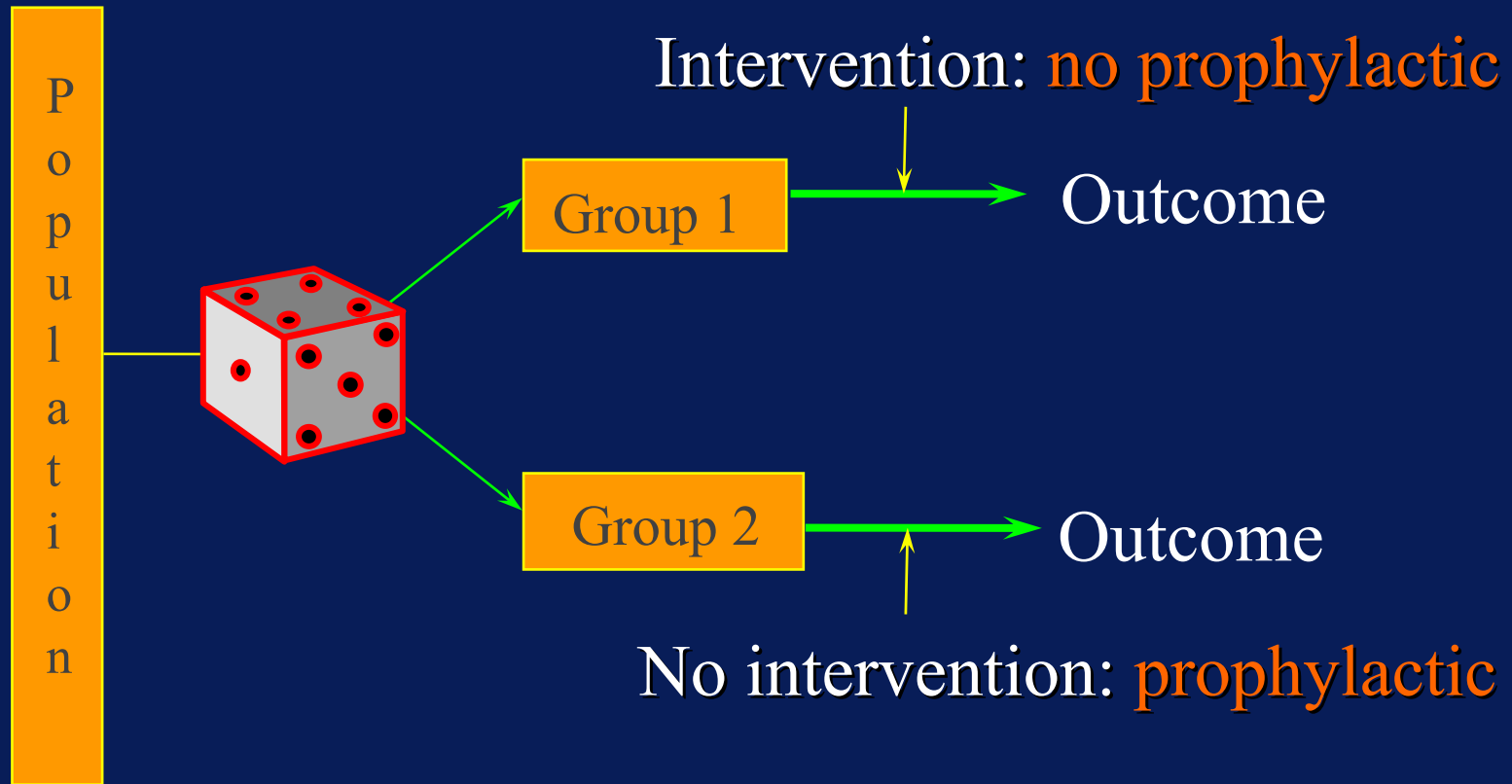
### Grade 4

- Debilitating bleeding including retinal bleeding with visual impairment
- Non-fatal CNS bleeding with neurological signs and symptoms
- Bleeding associated with haemodynamic instability (hypotension, >30 mm Hg change in systolic or diastolic HP)

Wandt et al, BMT 2006, 37, 387  
Therapeutic strategy in autografts

- 106 patients , 140 autografts (consecutive)
- Therapeutic only strategy for bleeding (when more than petechiae)
- 19% transplants minor-moderate bleeding
- Reduction in platelet transfusions
- 1/3 transplants without platelet transfusion
  
- Schaefer-Eckart et al, Blood 2006, A577  
RCT - Therapeutic strategy in autografts

# TOPPS: UK Trial of prophylaxis vs no prophylaxis



This trial is really about ‘individualising’ platelet transfusions

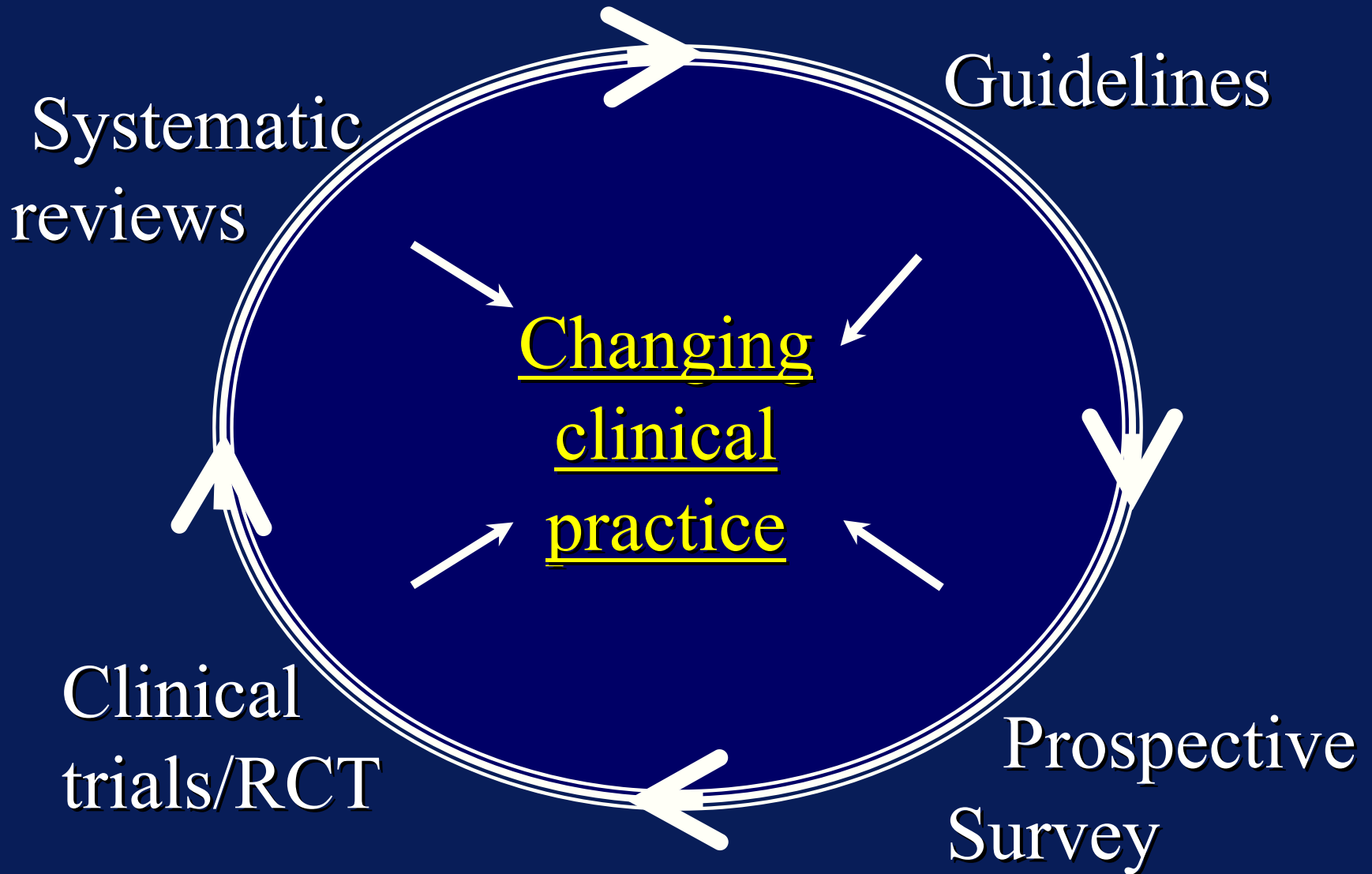
# Current progress

- Started one centre end 2006
- 4 recruiting centres now as planned
- >90 patients randomised - feasibility
- 2 withdrawals
- 50% autografts, others RIC, consolidation chemotherapy AML

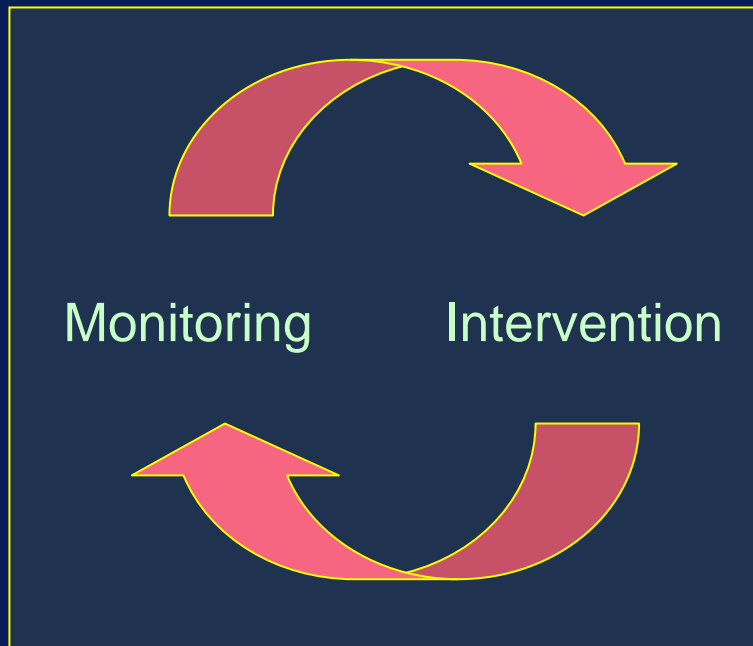
# Variation - NCA of platelet transfusions

- Hospitals provided data on 40 consecutive patients receiving platelet transfusions including haematology patients
- 2125 platelet transfused haematology patients - 72% usage as prophylactic transfusion
- Poor compliance e.g. use of a threshold count  $>10 \times 10^9/L$  for 60% of prophylactic transfusions in haem patients without risk factors indicating the need for a higher threshold

# Research Cycle



# Interventions to alter Transfusion Practice



- Guidelines
- Education
  - » Group
  - » Individual
- Reminders
  - » Computerized
  - » Paper
- Audit / Feedback
- Audit / Approval

# Systematic reviews: *Wilson et al., Transfusion 2002; Tinnmouth et al., Archives of Internal Medicine 2005* - Interventions Reported:

- Guidelines – 12
- Education – 9
- Audit / Feedback – 9
- Audit / Approval – 4
- New transfusion form - 7

## Single Interventions

- Guidelines -2
- Audit / Feedback – 1
- Audit / Approval – 1
- Education - 1

## Multiple Interventions

- 14 studies

# Single vs. Multiple Interventions

- Overall range of reduction similar for studies using single and multiple interventions
    - » Single interventions – 14 to 55%
    - » Multiple interventions – 9 to 77%
- ... but 3 of 4 studies that did not show a reduction in utilization for **all** blood products studied were single interventions

# Quality of Identified Studies

- 24 studies included in 2 systematic reviews
  - » 22 Before-And-After Studies
- Before-and-After Studies
  - » Secular changes (selection bias)
    - Only 1 study had concurrent controls
  - » Mixed retrospective and prospective data collection (information and instrumentation bias)
  - » Act of monitoring may change practice
- Duration of Monitoring: 3 -12mth ie *sustainability*
- Publication bias – Negative studies not published

# Conclusions from Systematic Reviews

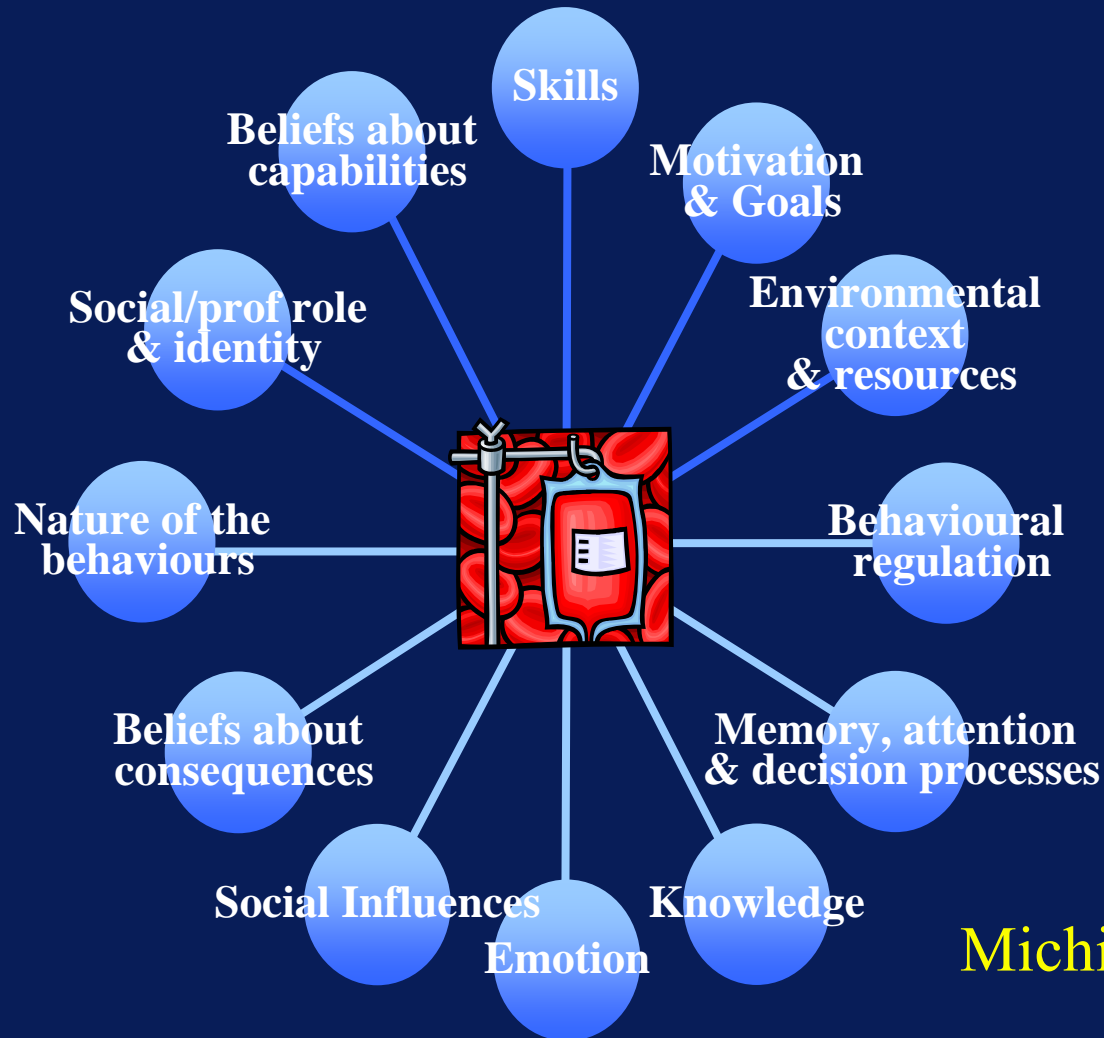
- Based on identified studies, interventions seem to work
- “Strength” of conclusions limited by quality of published studies and publication bias.
- Unable to determine the relative effect of individual or multiple interventions
- Background of expanding literature on evidence-based implementation

# Next steps – evidence based implementation

More rigorous methods to evaluate uptake of research findings and to develop a theory based intervention to promote improvement in transfusion

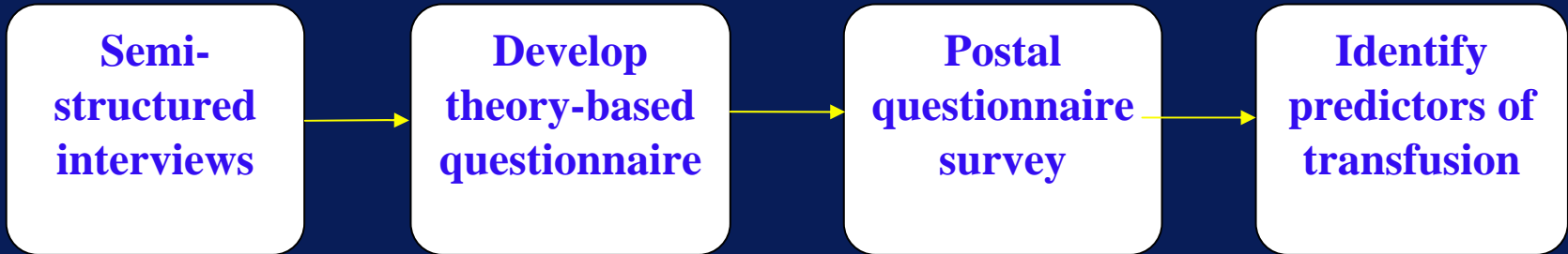
- Transfusion practice is a form of behaviour
- Psychology is the scientific study of behaviour
- Theories from psychology predict behaviour and develop behaviour change interventions

# Theoretical phase to identify determinants of transfusion behaviour and the barriers



Michie et al. (2005)

# Summary

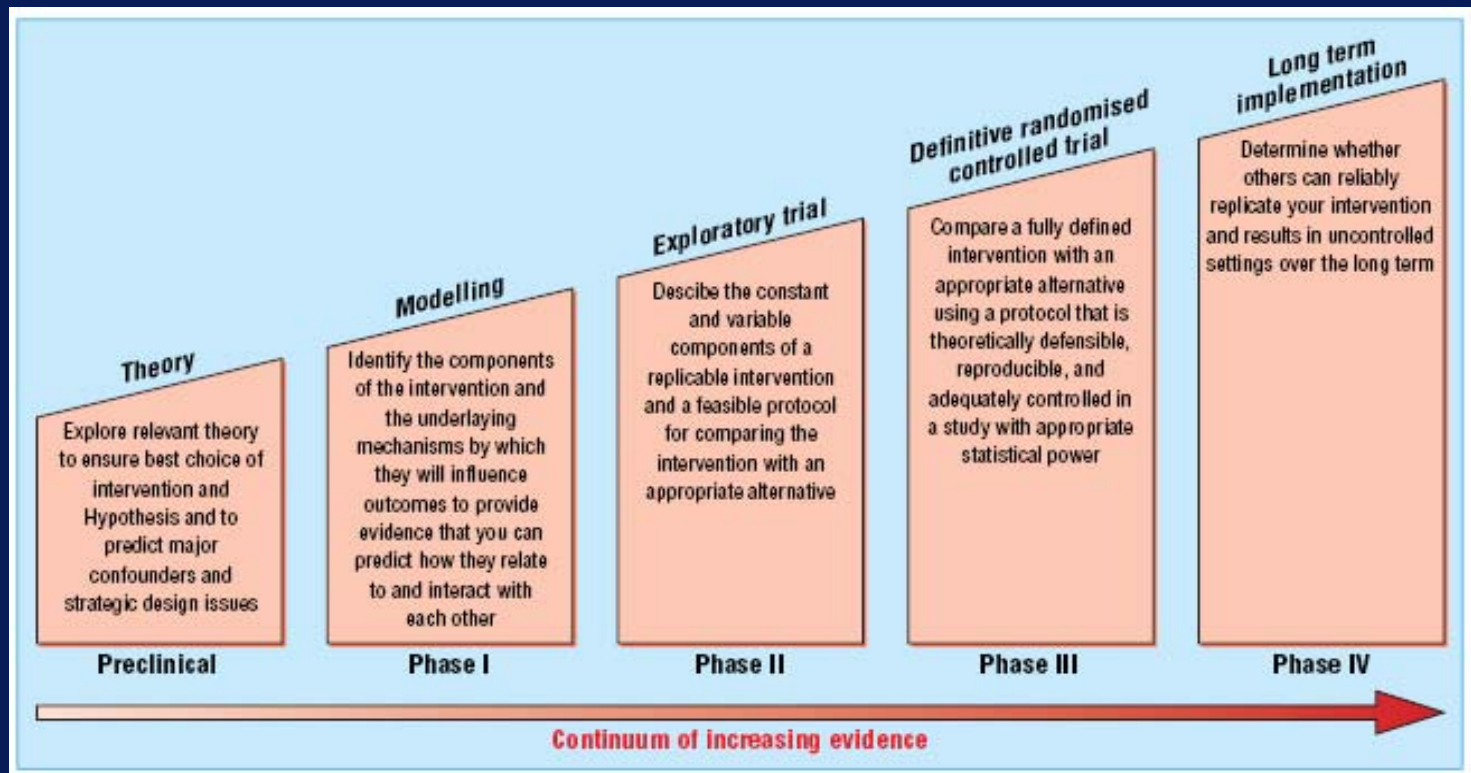


# Results

Semi-structured interviews – completed adult ICU, planned neonatology

Postal survey – 130 replies being analysed

# MRC framework – implementation research & application to transfusion



Sequential phases of developing randomised controlled trials of complex interventions

Medical Research Council (2000); Campbell et al. (2000)

# Platelet Process Improvement Project (PPIP) clinical study

Comparison of platelets stored for 2-5  
days vs 6-7 days  
in  
preventing and treating haemorrhage  
in thrombocytopenic patients

# SHOT: Bacterial contamination clinical reports 1995-2005 (n=31)

- Platelets = 27;  
red cells = 4
- 7 deaths - 6 due to  
contaminated platelets
- 25/27 platelets  $\geq 3$  days  
old
- Predominant cause of  
post- transfusion  
infectious complications



# Background to study

- Without bacterial testing platelets stored 5 days
- With bacterial testing, storage extended to 7 days
- NBS already does this during shortages eg extended bank holidays, but not routinely
- The EU Directive and BSQR allow 7 days storage in conjunction with a bacterial detection system

# Platelet Process Improvement Project (PPIP) clinical study

Comparison of bacterially tested platelets stored for 2-5 days vs 6-7 days suspended in plasma

- To assess in vivo efficacy of extended shelf life platelets in plasma for range outcomes
- Type: randomised block, non –inferiority, matched pairs, cross-over design
- Patients: adult thrombocytopenic haem-onc patients requiring platelet transfusions

# Progress

## Temporary suspension

- Bacterial transmission occurred following transfusion of a 6 day platelet which tested negative on bacterial screening
- Study on extended shelf-life platelets in US also stopped

Thanks – and finally...!





*Three Choirs Vineyard, Gloucestershire*

# Acknowledgements

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C Hyde, A Tinmouth, J Grimshaw

