



**DART trial committees  
- what are they all for?**



# Large trials



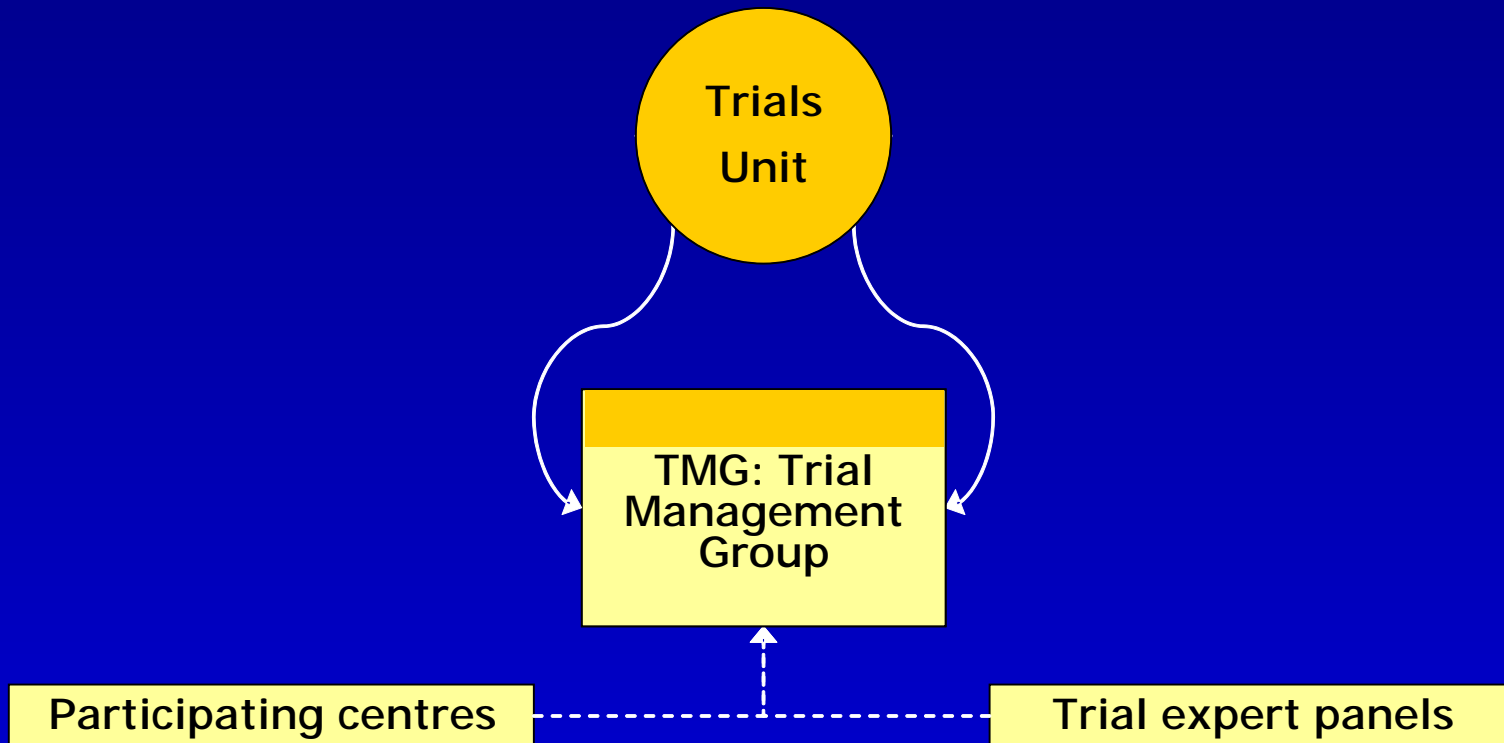
- Typical characteristics of large trials
  - lots of patients
  - followed for a long time
  - to clinical endpoints
  - costing ££££££££
- understandable reluctance on the part of trial sponsors to leave everything that goes on in such trials just up to those running them day-to-day (the **Trial Management Group**)



# Relationships



Sponsor/Funder





# What is needed?



- independent oversight of management
  - make sure trial is on track, and decisions being made are protecting the integrity of the trial
  - **Trial Steering Committee, TSC**
- independent assessment of clinical events that might be trial endpoints
  - particularly important for open trials
  - **Endpoint Review Committee, ERC**
- independent consideration of data from randomised groups
  - make sure trial is safe to continue
  - **Data [and Safety] Monitoring Committee, DSMC/DMC**



# Trial Steering Committee: TSC



- **role:** independent oversight of the trial
- **executive:** makes the decisions
- **membership:** ~10 people
  - independent chair
  - independent members
  - representatives from the TMG
- **meetings:** every 9-12 months
  - observers (non-voting) include representatives from funders, supporting pharmaceutical companies and members of the TMG



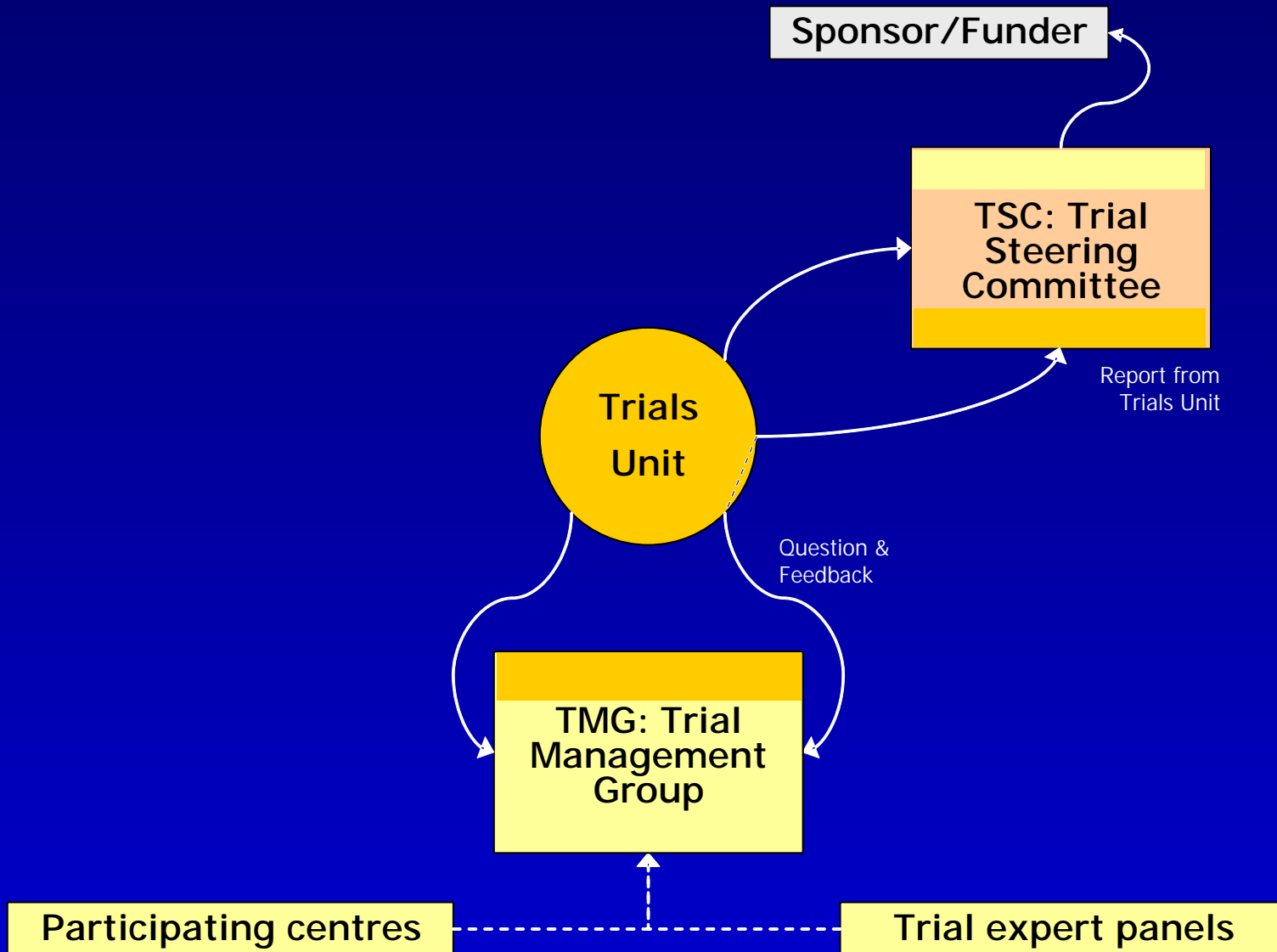
# TSC: examples from DART



- TSC decided to increase the number of patients by 300 to compensate for longer than expected accrual
- after the STI pilot, TSC decided to modify the design of the STI/CT randomisation
- TSC decided to stop the STI/CT randomisation, following advice from DSMC (see later)
- TSC approve DART substudies, all DART abstracts, conference presentations and manuscripts
  - make sure these don't compromise the main trial objectives



# Relationships





# Endpoints in DART



- Primary endpoint is new WHO 4 event or death
- Protocol contains criteria for presumptive and definitive diagnosis of every WHO 4 event
  - developed by DART team with aim of relevance and feasibility in Africa
- A patient has a “clinical episode”
  - clinical episode may clearly satisfy one of these WHO 4 criteria
  - or not!



# Where does it all go wrong?



- Patient has a “clinical episode” reported as one or more WHO stage 4 events
- Some problems
  - appropriate tests cannot be performed (eg CT scan without contrast, patient dies)
  - clinical episode is compatible with a number of different WHO 4 events which all get reported - as time goes on, the clinical picture becomes clearer
  - one clinician’s “event” is different to another’s (subjectivity of clinical endpoints)
  - episodes get reported which shouldn’t (clearly don’t meet criteria)



# Why is this a problem?



- Randomised groups are compared on the basis of these primary clinical endpoints
- Getting these wrong may give the wrong answer
  - particularly important in “open” (not blinded) trials, as clinicians may be more or less likely to report events in one arm due to prior beliefs about efficacy  
[BIAS]
- Getting these wrong may give no answer
  - having lots of random incorrect endpoints will dilute any difference between randomised groups which may not then be statistically significant [RANDOM ERROR]



# Endpoint Review Committee: ERC



- **role:** review all reported events which could potentially be primary endpoints and decide which to include in randomised comparison
  - all reported WHO stage 4 events, deaths
- **members:**
  - independent Chair
  - 2 other independent members
  - DART Project Leaders



# ERC meetings



- all deaths and WHO stage 4 events reported in DART are reviewed
- each has a clinical summary written
- Chair and 1 other independent member carry out “barndooring” every other month
  - barn door: very large - very obvious decision!
  - events which obviously meet criteria are accepted
  - events which obviously fail the criteria are rejected
- all other events, and any deaths not clearly HIV-related, go to a full ERC teleconference (~3-4 monthly)

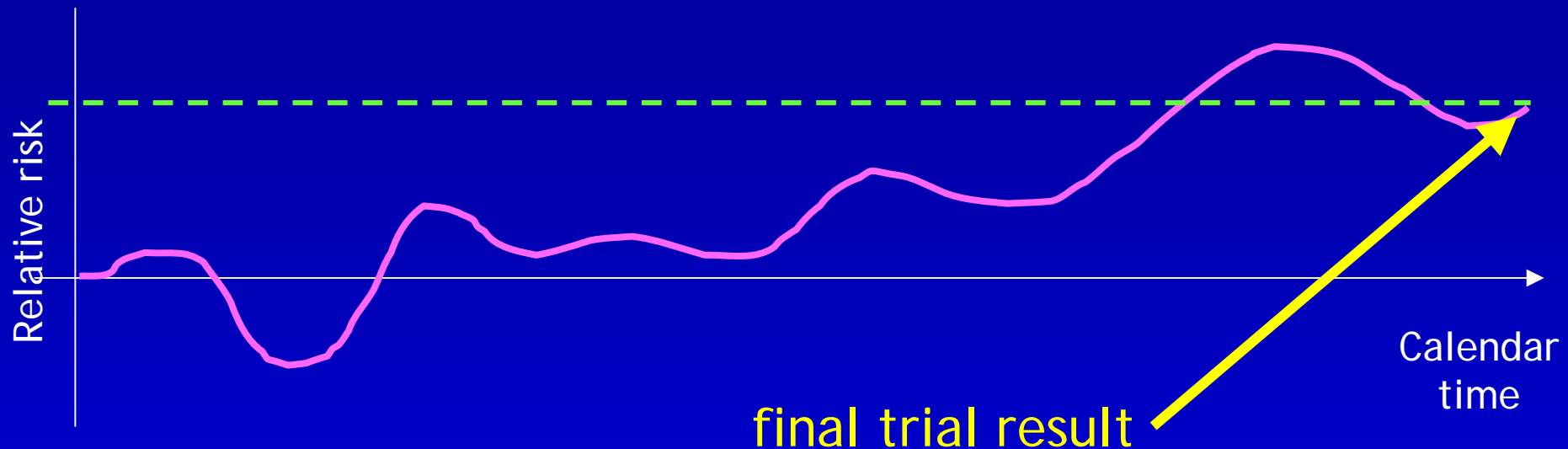




# Running a trial



- as a trial proceeds, endpoints occur, and evidence in favour of one arm or the other accrues
- this process is not as regular as you might imagine!

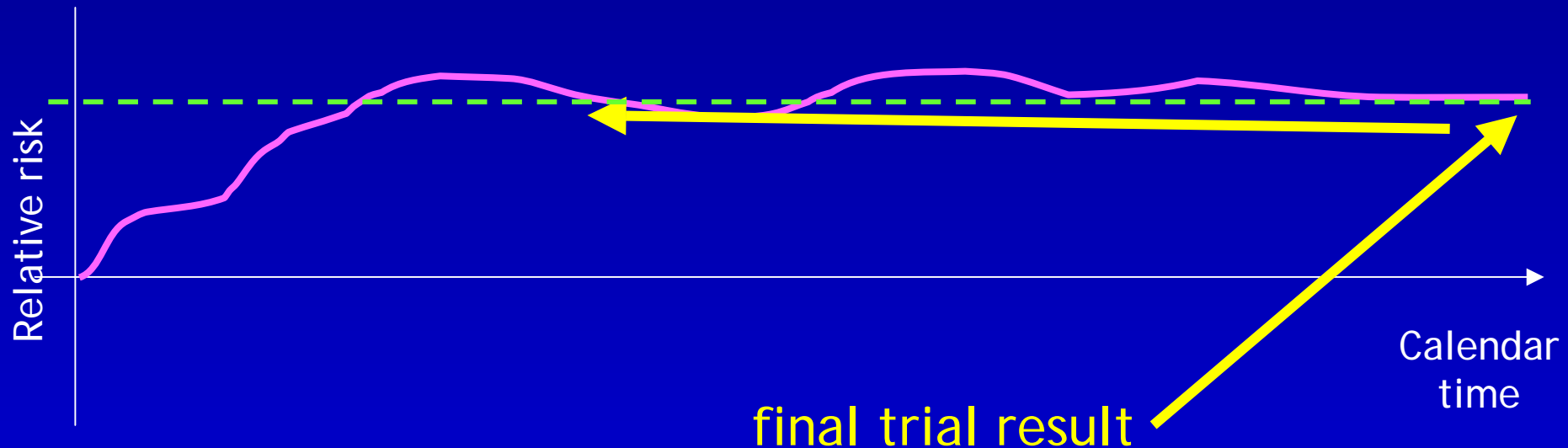




# Running a trial: to avoid



- sometimes things go better than anticipated, and the final result could have been known long before the planned end of trial
  - patients have received the inferior treatment for longer than necessary

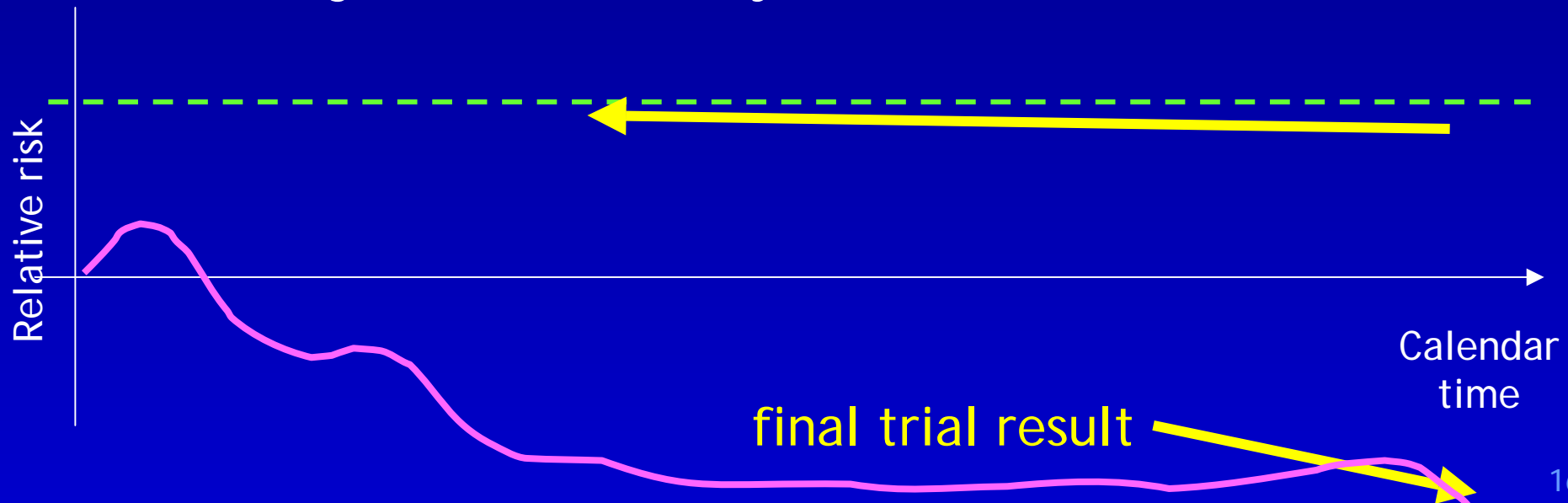




# Running a trial: to avoid



- sometimes one randomised group does much worse than anticipated, and this result could have been known long before the planned end of trial
  - patients have received the inferior treatment for longer than necessary





# Trial monitoring



- monitoring the comparison between randomised groups as the trial proceeds can stop trials carrying on when a definitive answer is already known
- problems
  - multiple statistical significance testing
  - bias



# Multiple testing



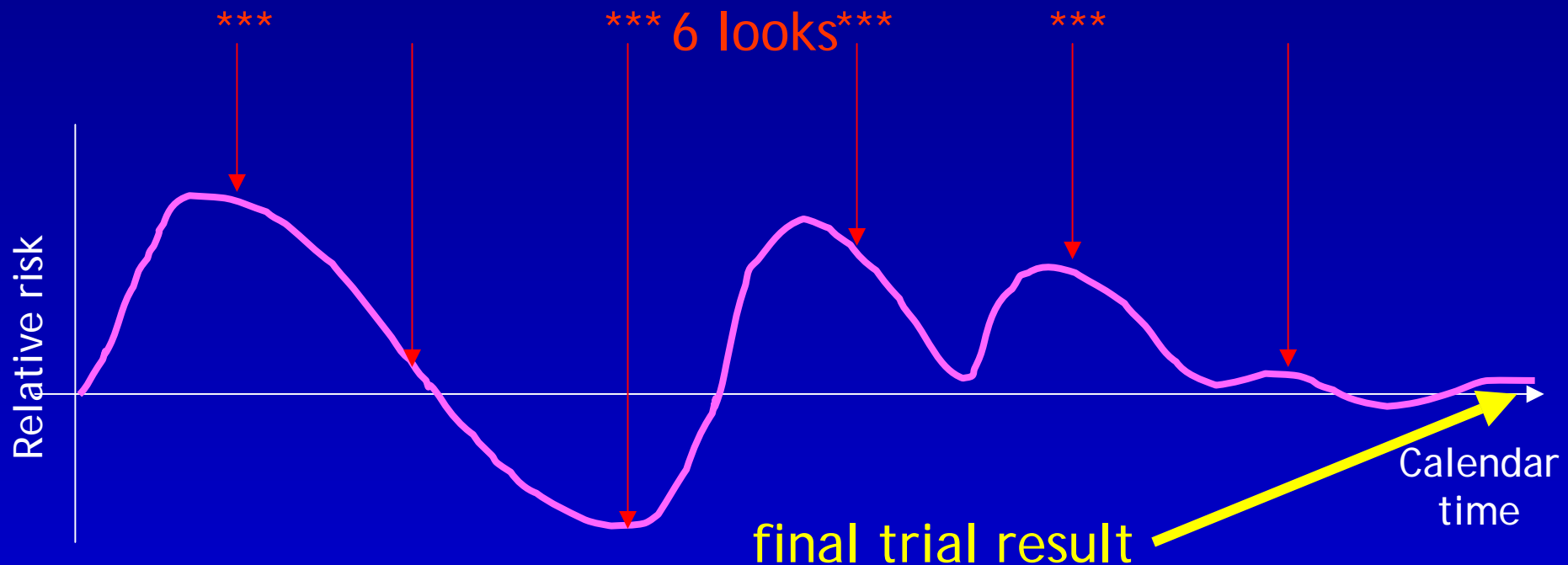
- even if there is no difference between groups, the more times you look, the more likely you are to “find” a difference just by chance





# Multiple testing

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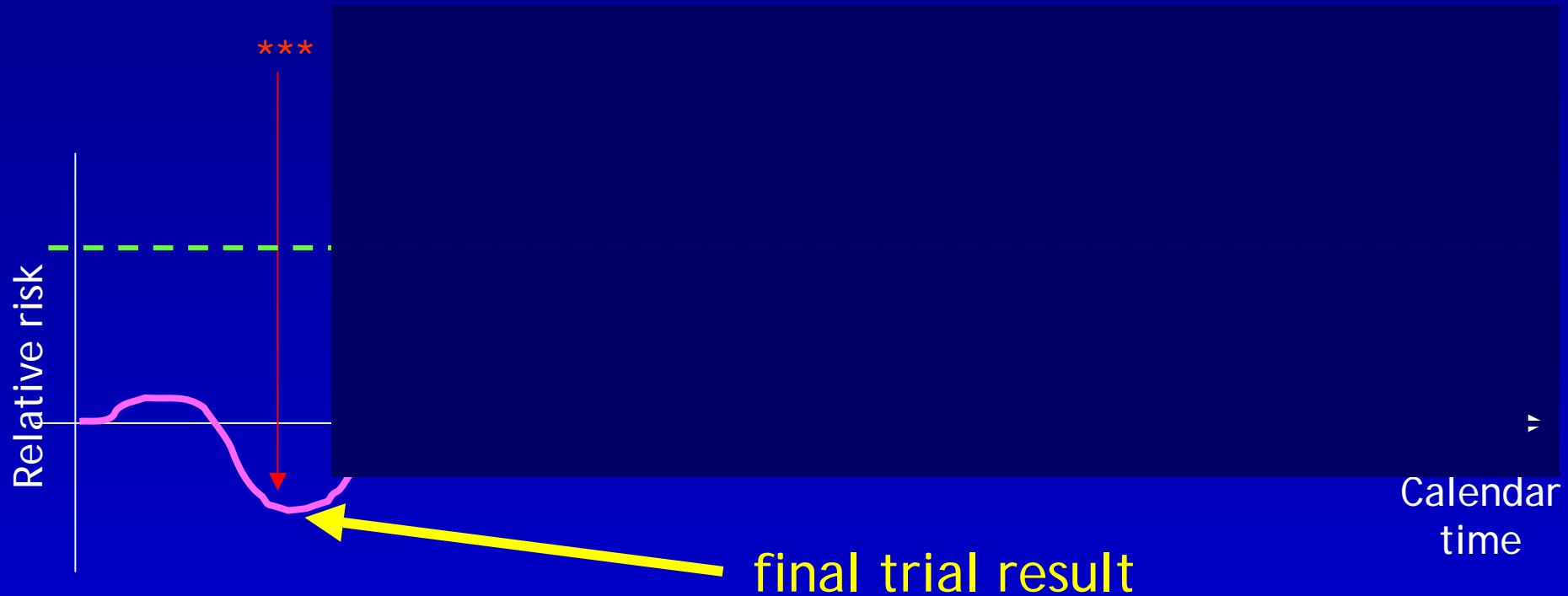




# Multiple testing



- even worse...





# Bias



- in theory, TMG could review the randomised comparisons at various times during the trial and decide whether to proceed or not
- it is impossible to exclude knowledge of current differences between randomised groups impacting on patient management, even if these current estimates are known to be imprecise
- modifies the intervention the trial is trying to assess: cause or effect?
  - self-fulfilling prophecy!



# DMC



- **role:** to review data according to randomised groups to make sure that there isn't sufficient evidence of harm or benefit such that the trial should be stopped
- **advisory:** advises the TSC what to do
  - TSC makes the decisions
- **members:** 3-5, ALL INDEPENDENT, expertise in
  - clinical trials
  - statistics
  - clinical medicine
  - DMCs



# DMC meetings



- **meetings:** usually before TSC
- receive a long (~150page) and detailed statistical report of the trial
  - by randomised group
- prior to DMC meeting, critical to have a large push on data cleaning, as you don't want decisions being made on the basis of incomplete or old data



# DMC meetings



- DMC consider the differences between randomised groups in primary endpoint(s)
- taking into account
  - multiple testing issues/chance variation
  - biological plausibility of differences
  - differences in other secondary endpoints
  - whether differences would change clinical practice if trial stopped now
- also raise other issues of trial management which in their opinion could impact on the primary comparison of randomised groups



# DMC meetings: format



- meetings usually have 3 sessions
- Administrative Session: independent DMC members only meet to discuss issues they would like to raise
- Open Session: independent DMC members, Trial Statistician, and trial Principal Investigators (PIs) meet so the trial PIs can update the DMC on relevant issues and challenges in the trial, and DMC members can seek clarification of issues raised by their report
- Closed Session: independent DMC members and Trial Statistician consider the data!



# DMC



- confidentiality is paramount: reports are collected and destroyed, and members are asked to sign a confidentiality agreement
- Trial Statistician is the only member of the TMG who attends the whole DMC meeting
- all contact with the DMC proceeds through the Trial Statistician to prevent potential contamination of the trial



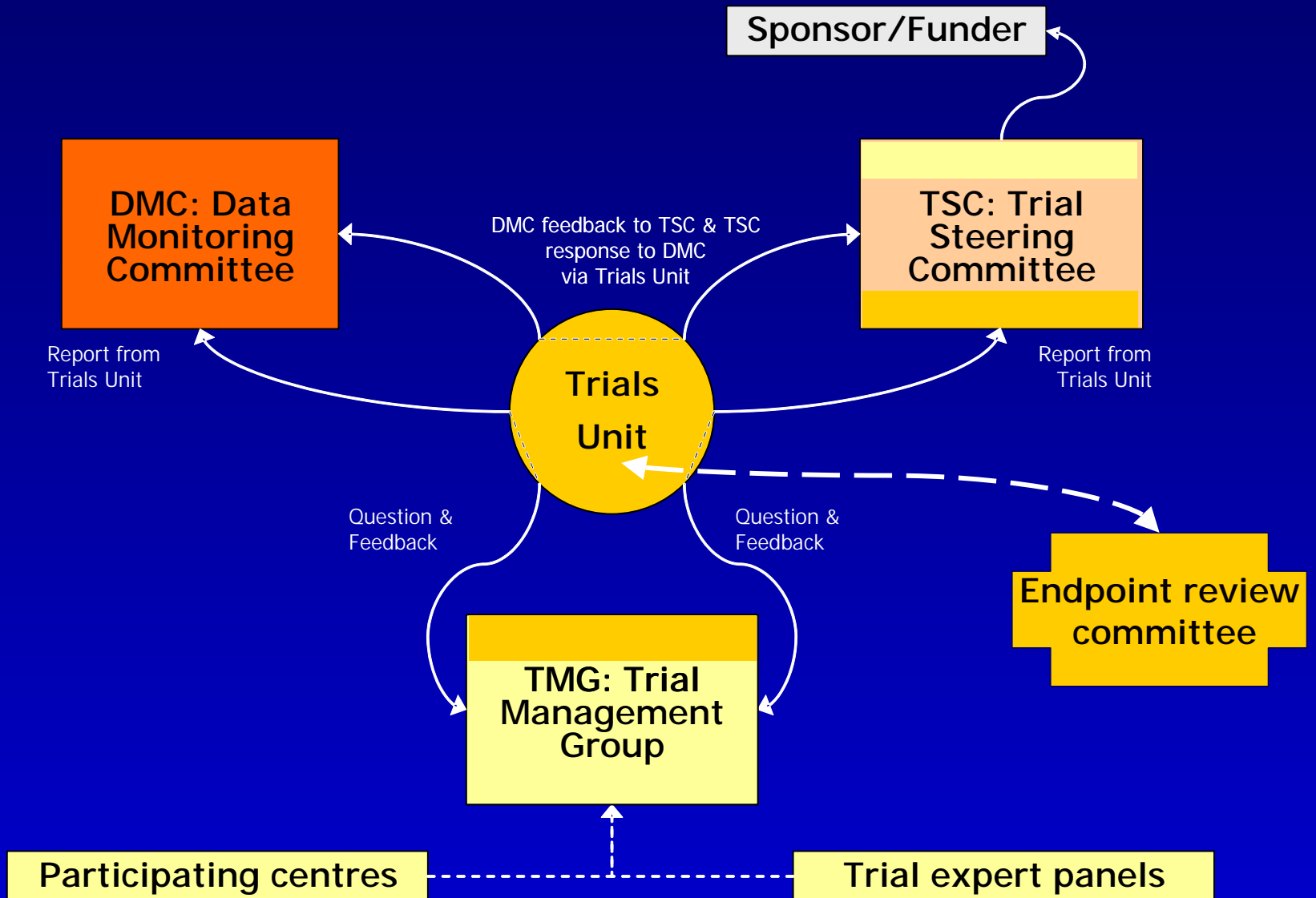
# DMC: then what happens?



- DMC write a report to the TSC
  - may recommend trial stop or be modified, or continue as planned
  - may raise other issues (eg delayed switch to second-line, pregnancies, overall creatinine decreases)
- TSC meets and decides what to do!
- TSC respond to DMC, telling them what they've done to address their issues
- DMC report sent to ethics committees



# Relationships





# Conclusions



- all these committees seem unnecessary and are a lot of work to manage

BUT

- they each have a unique role
- they each ensure patients are protected
- they each make sure the trial gets the right answer in the right amount of time