Reasons why physicians and statisticians are needed on a DMC

Jo Glover

Consultant Pharmaceutical Physician

Role of the DMC and its members

- According to EU and US regulatory Guidance, DMC is required in clinical trials where high morbidity/mortality disease or vulnerable subjects are involved
- DMC roles
  - To protect the safety of trial subjects
  - To protect the scientific integrity of the trial (ethical issues in involving patients if trial invalid)
  - To review unblinded results of interim analysis and make recommendation on action to be taken
- Textbooks on DMCs mostly written by Statisticians (including regulatory guidance, DMC procedures, study integrity issues, analytical methods for interim efficacy analyses, analytical methods for safety analyses)

Composition of DMCs

- Most comprise two or more clinicians (experts in the therapeutic area), maybe an industry physician as drug safety expert, a voting statistician and an ethicist
- Industry physician has different skills to clinical experts (experience in clinical trial design, operations, data collection, MedDRA, data analysis, regulations)
- DMC is provided data by an independent statistician: may or may not attend closed sessions but non-voting
- Voting statistician can advise on issues of study integrity, can interpret interim analysis of efficacy and can perform analyses of safety data

If the statisticians can fulfil these DMC roles, are physicians needed?

Why are there more physicians on DMCs than statisticians?

H0 = Physicians make no significant difference to the functioning of a DMC

Complementary roles of physicians and statisticians

Considering the roles of the DMC:

- Ethical issues in vulnerable populations – mostly realm of physicians
- Scientific integrity of trial conduct - both have a role
- Efficacy interim analysis - mostly the realm of statisticians
- Safety analysis - most the realm of physicians
- Risk/benefit analysis - both have a role
- Making recommendations to the trial sponsor - both have a role

Ethical issues in vulnerable populations

- Individuals who cannot protect their own interests eg minors, pregnant women, physically handicapped, mentally disabled
- Issue in vulnerable population is to protect population from adverse outcome of study participation. Example: Congenital abnormality/foetal death in an IVF study
- Ethical issues can’t be pre-defined or analysed
- Subjective judgement required, based on physicians’ experience of disease area and of managing patients

Scientific integrity – study design

- DMC assesses quality of study protocol up front and comments on important issues of design, including location and number of trial sites

Physician	Statistician
• Appropriate diagnostic techniques to define population • Definition of prognostic features in inclusion/exclusion criteria • Whether control reflects current treatment practice • Effect of geographical area on outcome • Relevant size of treatment effect	• Appropriate analyses for endpoints • Proposed sample size/treatment effect/power • Procedures for interim analysis (including limiting unplanned interim analyses!) • Randomisation, stratification and blinding procedures

Scientific integrity/Data quality

- Before analysing results at each interim look (safety or efficacy), DMC assesses quality of data provided:

Physician	Statistician
• Dates of most recent SAE reports (SAE database – 1 week prior) • Quality of SAE reports, including narratives • Consistency between clinical and SAE database	• Proportion of expected clinical data points present (clinical database – 6 weeks prior) • Internal consistency between different sources of same data eg AEs leading to death and number of deaths

Scientific integrity/Data quality cont'd

Physician	Statistician
• Clinical importance of differences in demog/dis history between arms • Clinical importance of protocol deviations occurring • Adherence to incl/excl criteria and procedures if recruitment rapid (may recommend limits) • Importance of any changes to clinical protocol during study (Roles for clinical experts and industry physician)	• Size of differences in demography/disease history between arms • Proportion with protocol deviations on each arm • Importance of any changes to planned analyses during study period • Evidence of maintenance of blind of Sponsor study staff

Interim efficacy analysis

- Interim efficacy analysis, if included, should have time point, methods and decision-making rules pre-specified in protocol so what roles do DMC members play?
- May be straightforward advice from statistician to Committee when analysis endpoints have clearly been met or clearly not
- Less straightforward when results are equivocal eg
  - Borderline results of primary analysis and opposite or mixed results in any secondary analyses
  - Borderline results of primary analysis and data appear poor quality or incomplete (eg inconsistent death data for OS)
  - Stratified analysis conducted but strata (with small interim sample size) not balanced in size
  - Early difference between treatments in survival analysis but KM curves come together or even cross eg early drug toxicity but later possible evidence of efficacy

Interim efficacy analysis cont'd

Physician	Statistician
• If results of survival analysis change over time, is it acceptable to expose patients to early risk for later possible gain in context of other treatment options? • How should existing patients be managed if DMC recommends study stop (all withdrawn, allowed to stay on study if they wish, allowed to stay on study if beyond risky time zone….)? • Will safety data be mature if study stopped for efficacy? • If study not stopped, should any aspects of protocol be changed to improve efficacy/reduce risk?	• If results of survival analysis appear to be changing over time, how will they look as data mature? Might early stop for futility or efficacy be premature? • If study not stopped, could aspects of protocol be changed to improve efficacy/reduce risk or would that bias results? • What blinding issues might occur if DMC recommends change to protocol?

Remember the retrospectoscope!

Consider and document all possible medical and statistical aspects of DMC decision to stop a study before acting

Interim assessments of safety

- DMC receives unblinded TFLs for AEs/SAEs/fatal AEs, vital signs, labs, ECGs, study-specific safety parameters and dosing data from clinical database plus output from SAE database
- In most conditions, SAE database output is more important
- In fatal/LT conditions, fatal SAEs most important
  - Fatal SAEs must be viewed in context of disease-related deaths ("All deaths")
- In vulnerable population studies, other SAEs may be most important eg congenital abnormality/fetal death in pregnancy
- Consider how to present results from both databases for best/easiest review: with or without statistical analysis?

AE outputs from clinical database

- Usually AEs tabulated by MedDRA SOC and PT in descending order of frequency (number of events or % patients reporting event at least once) and by treatment arm
- Statistician may want analysis of difference in incidence between treatment arms eg p values
- Issues with this approach:
  - AE table often lists 100s of PTs eg 1000-patient cancer study
  - Number of patients reporting each event usually small so difference is non-significant
  - Multiple testing will lead to some differences
  - Statistically significant is not clinically significant

AE outputs from clinical database

Physicians prefer to use clinical judgement based on experience of the disease area/underlying pathology because

- Results (in an open study) or differences between treatment arms need to be viewed in context of expected patterns of AEs in that disease state/drug class
- Clinically important may not be statistically significant eg non-significant increase in “sudden death” vs statistically significant increase in “skin rash” in oncology

Detailed knowledge of MedDRA and pathophysiology is required to find patterns/differences in toxicity because, for example:

- Same event may be coded differently in MedDRA so PTs should be added together to calculate frequency eg reduction in neutrophil count coded as “Neutropenia” in Blood SOC or “Neutrophil count decreased” in Investigations SOC

AE outputs from clinical database cont'd

- If one signal exists, more important clinical associations should be explored eg is decreased neutrophil count associated with pyrexia ("febrile neutropenia" in Blood SOC) or infection (whole SOC or bacterial/viral/fungal infections)?
- Clusters of events indicating unexpected toxicity will not be recognised by statistical analysis eg thromboembolic events may include
    - "deep vein thrombosis" or "arterial embolism" in Vascular SOC
    - "pulmonary embolism" in Respiratory SOC
    - "ischaemic stroke" in Nervous System SOC
    - "myocardial infarction" in Cardiac SOC
    - "sudden death" in General SOC

AE outputs from clinical database cont'd

- Different treatment arms may have different duration of exposure due to protocol design, affecting assessment of AEs expected to occur over time eg incidence of TE events in oncology study where targeted therapy continues but control chemo is of fixed duration

➔ Clinical experience needed to spot unusual events or patterns of events and to judge clinical significance of differences between treatment arms but

➔ Statistician can assist using analysis eg apply MedDRA SMQ once pattern is identified, estimate duration of exposure

Lab data, vital signs, study-specific parameters from clinical database

- Even larger volumes of data: scope for statistical analysis
- Descriptive analyses and plots are especially useful to allow review of trends in large volumes of data eg plot of summary stats of vital signs, box and whisker plots of labs
- Pre-specified change criteria can be applied to analyse some parameters but
  - Clinical relevance of any patterns/differences detected still requires physician interpretation eg significance of change in bp
  - Some lab abnormalities more important than others eg fall in WBCs vs bicarbonate
  - Some groupings of lab abnormalities indicate particular diseases/toxicities eg different patterns of LFTs
  - Individual severe abnormalities may be more important than overall population trends (and must not be lost in analysis)

SAE database output

- The most important and up-to-date data for the physicians
- SAE databases have set outputs (line listings and CIOMS I forms) and custom reports available
- For high mortality disease states, provide separate listing of fatal SAEs by treatment arm
- Must be unblinded and sorted by treatment arm
- For larger studies/disease states where many SAEs expected, tabulation of frequency by SOC/PT and treatment arm very useful to spot patterns
- Unblinded statistician should check data on SAEs and fatalities in clinical and SAE databases are generally consistent (check whether any differences due to lack of data cleaning or time lag)

Interpretation of SAE data

- Same limitations of statistical analysis apply as for AEs
  - Single unusual or irreversible event can be more important than multiple others, requiring clinical judgement
  - Assessment of importance of SAE may depend upon reading the narrative for clinical detail eg sudden death
- Analysis must occur in the context of the disease state and overall toxicity profile
  - Individual SAE or type of SAEs may stand out as unusual in the disease state, based on clinical judgement
  - Increase in one fatal SAE type may not cause study termination if overall death rate lower (assessment requires “All deaths” data: unscheduled primary endpoint analysis must be avoided)

Risk/benefit assessment

- While regulators have efficacy and safety data at time of MAA, DMCs don't usually have both
- Even if interim efficacy analysis data are available, safety data likely to be immature
- DMC required to make decisions affecting large number of lives based on incomplete data
- Decisions at time of interim efficacy analysis are relatively easy because pre-determined
- Decisions based on safety issues are definitely not easy because
  - Pre-determined limits not often set
  - Statistician can provide assessment of statistical significance for guidance but final decision based on clinical judgement
  - Subjective decision as to whether excess of a certain toxicity on one arm is sufficiently clinically important to recommend stopping the trial

In conclusion

- Clear need for statistical and clinical approaches in a DMC
- More than one physician is needed to discuss/agree recommendations due to obvious risks of a major decision, potentially affecting lives and sponsor funds, based on personal judgement
- Physicians and statisticians need to be of sufficient experience and confidence to stand up to scrutiny by Sponsor, regulators and patient groups/lawyers

H0 is invalid: Physicians can make a significant difference to a DMC!