SOCIETA'
DI SCIENZE
FARMACOLOGICHE
APPLICATE

SOCIETY
FOR APPLIED
PHARMACOLOGICAL
SCIENCES

BIAS
Biometristi dell' Industria ASsociati

Summary of

DMC Meetings
How to avoid common traps ?

Giacomo Mordenti
Global Biometrics Head, Livanova

SOCIETA'
DI SCIENZE
FARMACOLOGICHE
APPLICATE

SOCIETY
FOR APPLIED
PHARMACOLOGICAL
SCIENCES

BIAS
Biometristi dell' Industria ASsociati

Objective of this presentation

To provide some hints on how to efficiently manage your DMC

Once upon a time there was a….

… clinical trial

➡ **Drug was recently approved worldwide**

➡ **Its safety profile was well established**

➡ **Regulators requested an additional trial in small population, not explored in the main development**

➡ **A Data Monitoring Committee was to be established**

Goal: review safety data on ongoing basis

➡ **A DMC Steering Committee was established as well**

Goal: receive DMC recommendation and endorse decisions

➡ **DMC members were chosen:**

- ✓ **academic experts in study population**
- ✓ **limited experience as DMC members**
- ✓ **from US and EU**
- ✓ **freelance statistician very experienced in DMC**

- **Protocol & DMC Charter**
  - **ready in close time frame**
  - **high-level**

- **Company put pressure given the challenges in recruitment in the population**

- **The trial got all the green light and then… it started**

BUT

- **Recruitment was much slower than expected**
- **After 1 year company decided to have the 1st DMC meeting despite the min number of subjects was not reached (approx 20 rather than 50).**
- **But anyway, 1 year after FSI, the statisticians started preparation of the SAP, as in three months the DMC would have met.**
- **Programming developed the programs and output (more than 1000 pages) was ready in time.**

Before the meeting

- ➡ One marker was missing in the output
  - not a safety marker
  - it was added during SAP development to please one of the DMC experts
  - could potentially unblind the team, at trial start the team decided to postpone the marker reading at the end of trial

- ➡ As the SAP was done 1y after FSI, the biostatistician was not involved in the initial discussion and he did not realize it at the time of SAP development

First DMC meeting

- Started with the wrong feet as the team had to apologize for missing information
- The meeting was over the phone as some of the experts were in US
- The open session was dominated by administrative (content of amendments, recruitment, etc.) & safety information

After the closed session, DMC gave their recommendation.

Study could continue given that the company would have provided additional information within 4w

The missing marker was to be provided ASAP

The output (roughly 1000 pages for less than 20 subjects) was not complete, additional information was required.

Plots were to be used to assess presence of outliers and trends

DMC SC Safety representative argued vs DMC that the amount of information was as planned, except for missing marker and that hundreds of subjects are treated every day without any safety issue.

This caused the DMC to become more "defensive" and the discussion was cut.

But the problem was that misunderstanding was generated which started to affect reciprocal trust

2nd DMC meeting – 4w later

- DMC got approx 1500 pages of output (still approx. 20 subjects)
- DMC claimed the presence of safety issues (unexpected safety signals) asking for the trial to be put on-hold
- Discussion was hot and long.
- Agreement: study was not to be put on/hold given that the company would have provided additional information

3rd DMC meeting – 4w later

➡ **DMC got all the information requested**

➡ **BUT they got too much output**

➡ **DMC requested to get patient data listings**

4th DMC meeting – 8w later

➡ **DMC got only patient data listing**

➡ **They felt reassured**

➡ **Trial could go ahead !**

What was the price?

➡ **CRAs, DM, Biostatistics and Programming got nuts!**

➡ **The company risked to have a simple trial turning into a nightmare**

Biostatistics and Programming had to face an unexpected peak of activity blocking 3 to 4 FTEs for a period of 3 months in order to satisfy DMC requests all of this in continuing emergency

DMC lost confidence in the company expertize to manage such a kind of trial. As suspicion increased, DMC became more rigid and less "reasonable".

Clinical Operations and DM had to implement protocol amendment, database and eCRF amendment, chase subjects retrospectively with huge amount of efforts and resources

The relationship between DMC and DMC SC was somehow compromised with the result of rigidity

What could be done better ?

REWIND

< <

How to avoid common traps during DMC meetings ?

Who is the DMC? Usually composed by 2 to 3 clinicians in academy

They can be very used to run DMC or not at all!

- **If they are used, they usually think they know it all**
- **Otherwise, they will try to apply their common practice in hospital to the output and decision making process**

The statistician is not part of the company (Either CRO or independent consultant used to run many DMC)

All of them they usually have no time to spend to thoroughly understand the study drug, the study protocol, Sponsor's needs, and Sponsor's specific requirement and expectations

Keep all of this in mind !

Put yourself in DMC shoes

Do not plan immediately for a bug amount of output

Focus on the basics => in case of small number of subjects put resources towards patient profiles rather than high number of tables with high number of subgroups

Use informative plots

Do not let others lead the DMC meeting agenda.

You are the biostatistician, you are there to guide the DMC members on how to read the output and what you are going to deliver them

Take time to educate them!!

Use as much as possible clean data

DMC are usually not statistician nor programmers and the independent statistician may not have the strength

Any strange or bizarre data may create suspicion and decrease trust in company capabilities

Ensure that DMC members have the possibility to know each other and also to know DMC SC members

A good face to face discussion and hand-shake will not ruin the company

As Biostatistician, do not let the others take your place

Stand and take your responsibilities

And….

Be reasonable

Put yourself into the DMC members shoes

It will be clear what you have to deliver and how