Stopping rules in First entry into human studies

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WHY

New requests by regulatory authorities after TGN 1412 tragedy – London 2006

→ Improve decision making process in dose escalation

→ Using risk assessment & minimization strategy

HOW?

Needs:

- Standardisation of quotation …through accurate and relevant «**Grading**»
- Relevant method to support «**Stopping rules**»
  - Individual level
  - Group/cohort level

SCOPE

- First-in-Human dose escalation studies
  single & multiple dose
- Healthy subjects

Current available guidelines (1)

Nothing relevant and accepted fitting well to healthy subject participating in FIHs

1. **WHO** Recommendations for grading Acute & subacute toxic effects *WHO Handbook for reporting results of cancer treatment* (1979)
2. **NCI** Common Terminology for Adverse Events (CTCAE v3 Aug 2006)

→ Only applicable to oncology

Current guidelines available (2)

3. **NIH** Division of **AIDS** (Dec 2004) : *Table for grading the severity of adult and paediatric adverse events*

4. **FDA** Guidance for Industry (Sept 2007) : *Toxicity grading scale for adult and adolescent volunteers enrolled in preventive* **vaccine** *clinical trials.*

→ controversy in-between organizations (2005)

→ not relevant enough to healthy subjects

Needs of relevant proposals

CPI proposals .../...

Preambule: definition & wording: Adverse Event or Finding

Adverse Event (ICH definition):

« any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship to this treatment ».

Preambule: definition & wording: Adverse Event or Finding

- Clinical event = **Adverse Event**
- Non-clinical (lab, EKG...) event = **Finding**

Quotation ?
Use the NIH/FDA grading

Grading: NIH/FDA 4-level scales of intensity:

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1. Grade 1 : mild : Does not interfere with activity
2. Grade 2 : moderate : Interferes with activity; no treatment excepted acetaminophen (limited amount)

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Use the NIH/FDA grading

Grading: NIH/FDA 4-level scales of intensity:

1. Grade 1 : mild : Does not interfere with activity
2. Grade 2 : moderate : Interferes with activity; no treatment excepted acetaminophen (limited amount)
3. Grade 3 : severe : Prevents daily activity or requires treatment (*or medical intervention - FDA*)

Quotation ?
Use the NIH/FDA grading

Grading: NIH/FDA 4-level scales of intensity:

1. Grade 1 : mild : Does not interfere with activity
2. Grade 2 : moderate : Interferes with activity; no treatment excepted acetaminophen (limited amount)
3. Grade 3 : severe : Prevents daily activity or requires treatment (*or medical intervention - FDA*)
4. Grade 4 : life-threatening : Emergency room visit or disabling or hospitalization

Firstly

Application to clinical AEs

1. Application to (clinical) AE (1)

→ quotation directly derived

from observed severity/intensity

or

from daily life consequences

Intensity	Grade 1	Grade 2	Grade 3
General definition	Does not interfere with activity		
Modulation and upgrading based on:	*number of episodes and/or*		
Headache	**Transient**		
FDA headache	*No interference with activity*		
NIH headache	*Symptoms causing no or minimal interferences with usual social & functional activities*		

Intensity	Grade 1	Grade 2	
General definition	Does not interfere with activity	Interferes with activity, no treatment except acetaminophen	
Modulation and upgrading based on:	*number of episodes and/or*	*duration of symptoms and/or*	
Headache	**Transient**	**Interferes with activity** ***e.g. several hours but less <12 hours.*** **no treatment except acetaminophen**	
FDA headache	***No interference with activity***	***Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity***	
NIH headache	***Symptoms causing no or minimal interferences with usual social & functional activities***	***Symptoms causing greater than minimal interferences with usual social & functional activities***	

Intensity	Grade 1	Grade 2	Grade 3
General definition	Does not interfere with activity	Interferes with activity, no treatment except acetaminophen	Prevents daily activity or requires treatment
Modulation and upgrading based on:	*number of episodes and/or*	*duration of symptoms and/or*	*significant associated malaise or general effects*
Headache	**Transient**	**Interferes with activity** ***e.g. several hours but less <12 hours.*** **no treatment except acetaminophen**	**Prevents daily activity** ***e.g. > 12 h, presence during the night.*** **or requires treatment**
FDA headache	***No interference with activity***	***Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity***	***Significant; any use of narcotic pain reliever or prevents daily activity***
NIH headache	***Symptoms causing no or minimal interferences with usual social & functional activities***	***Symptoms causing greater than minimal interferences with usual social & functional activities***	***Symptoms causing inability to perform usual social & functional activities***

	Grade 1	Grade 2	Grade 3
Vomiting	**1 episode**		
FDA Nausea/vomiting	**No interference with activity or 1-2 episodes**		
NIH vomiting	**Transient or intermittent vomiting with no or minimal interference with normal intake**		

Vomiting	1 episode	2 to 4 episodes/day or 2/day x 2 days	
FDA Nausea/vomiting	No interference with activity or 1-2 episodes	Some interference with activities or >2 episodes/24 hours	
NIH vomiting	Transient or intermittent vomiting with no or minimal interference with normal intake	Frequent episodes of vomiting with no or mild dehydration	

Vomiting	1 episode	2 to 4 episodes/day or 2/day x 2 days	4 episodes per day or 2 or more per day prolonged on several days
FDA Nausea/vomiting	No interference with activity or 1-2 episodes	Some interference with activities or >2 episodes/24 hours	Prevents daily activity or requires outpatient IV hydration
NIH vomiting	Transient or intermittent vomiting with no or minimal interference with normal intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (e.g. IV fluids)

Secondly

Application to non-clinical findings

Secondly

Application to non-clinical findings

Grade 1

2. Application to (non-clinical) findings (1) Grade 1

Most of findings = numerical and continuous variables

→ requires the use of a "threshold"

→ two approaches

1. **Existing recognized thresholds**: Disease definition (diabetes, HTA, anemia) or published rule (Hy's law / liver injury)
2. Use of a **relevant method** - discrimination between spontaneous variation or potentially significant findings -, to support threshold determination

2. Application to (non-clinical) findings (2)
Grade 1

CPI Proposal - The «Combined method (1)»:

An abnormality is qualified when ...

a value is out of "normal" range (reference values)

and is associated to

a variation from baseline superior to "change" range (reference changes).

... ***thus, exactly defines grade 1 threshold.***

(1) Sibille et al. Eur J Clin Pharmacol 1995; 47: 417-421

Examples

Example: ALT transaminase

Healthy young male subject database (1):

Ref. values: 10-**58** IU/L and Ref. changes: + **10** IU/L

Calculated threshold: **1.2 x Upper limit of NR**

1. Eur J Clin Pharmacol 1999; 55: 13

Example: ALT transaminase

Healthy young male subject database (1):

Ref. values: 10-58 IU/L and Ref. changes: + 10 IU/L

Calculated threshold: **1.2 x Upper limit of NR**

Application to worldwide NR(2): 0-35 UI/L

Grade 1 proposals:

1.2 ULNR

or **42 IU/L** (35x1.2)

1. Eur J Clin Pharmacol 1999; 55: 13

2.NEJM 2004; 351: 1548

Example: Creatinin

Healthy young male subject database (1):

Ref. values: 78 -**113** µmol/L and Ref. changes: + **15** µmol/L

Calculated threshold: **1.1 x Upper limit of NR**

1. Eur J Clin Pharmacol 1999; 55: 13

Example: Creatinin

Healthy young male subject database (1):

Ref. values: 78-113 µmol/L and Ref. changes: + 15 µmol/L

Calculated threshold: **1.1 x Upper limit of NR**

Application to NEJM worldwide NR(2): < 133 µmol/L

Grade 1 proposals:

1.1 ULNR or **146 µmol/L** (133x1.1)

… but ….

1. Eur J Clin Pharmacol 1999; 55: 13
2. NEJM 2004; 351: 1548

Example: Creatinin

Healthy young male subject database (1):

Ref. values: 78-113 µmol/L

…but **146 µmol/L** *this is* ***too high*** *in young healthy subject*

→ *113x1.1* → ***125/130*** *sounds more relevant.*

1. Eur J Clin Pharmacol 1999; 55: 13
2. NEJM 2004; 351: 1548

Conditions & Adaptation

- Accurate sampling and assay conditions
- Use the NR of the local lab of the Clinical Pharmacology Unit or of the NEJM.
- Any finding requires a control before validation
- Consider relative - % of Upper or Lower LNR -,
  or absolute value, as appropriate
- Adapt to the population (women, elderly …)

Secondly

Application to non-clinical findings

Grade 2 & 3

2. *Application to (non-clinical) findings (3)*

Grades **2 & 3**

- Rare existing recognized thresholds:
  - Disease definition: hypereosinophilia, rhabdomyolysis…
  - Published rule: Hy's law / liver injury
- No basis for relevant "method" of calculation

  → Club Phase 1: Consensus Approach on safety in HS
  - CPI senior investigators & sponsors (Working party)
  - Consideration to FDA and NIH guidelines

Examples

		Grades		
Parameter	Origin	1	2	3
ALT (ULNR)	CPI	1.2 to 3 ULNR	3 to 5	5 to 10

		Grades		
Parameter	Origin	1	2	3
ALT (ULNR)	CPI	1.2 to 3 ULNR	3 to 5	5 to 10
	FDA	1.1 to 2.5 ULNR	2.6 to 5	5 to 10
	NIH	1.25 to 2.5 ULNR	2.5 to 5	5 to 10

The values are similar in the 3 proposals

		Grades		
Parameter	Origin	1	2	3
Bilirubin (ULNR)	**CPI**	**1.3 to 2 ULNR if change from baseline > 10 mmol/L**	**2 to 2.5**	**2.5 to 3**

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Bilirubin (ULNR)	**CPI**	**1.3 to 2 ULNR if change from baseline > 10 mmol/L**	**2 to 2.5**	**2.5 to 3**
	FDA, if LFT normal	**1.1 to 1.5 ULNR**	**1.6 to 2**	**2 to 3**

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Bilirubin (ULNR)	**CPI**	**1.3 to 2 ULNR if change from baseline > 10 mmol/L**	**2 to 2.5**	**2.5 to 3**
	FDA, if LFT normal	**1.1 to 1.5 ULNR**	**1.6 to 2**	**2 to 3**
	FDA, if increase of LFT ***	***1.1 to 1.25***	***1.26 to 1.5***	***1.51 to 1.75***

**** Draft FDA guidance.*
Drug-induced liver injury (2007)

		Grades		
Parameter	Origin	1	2	3
Bilirubin (ULNR)	**CPI**	**1.3 (or # 35 IU/L) to 2 ULNR if change from baseline > 10 mmol/L**	**2 to 2.5**	**2.5 to 3**
	NIH	**1.25 to 2.5 ULNR**	2.5 to 5	**5 to 10**

NIH grade 2/3 limit seems too high and at risk

		Grades		
Parameter	Origin	1	2	3
Platelets decrease (giga/L) assuming no platelet cluster	**CPI**	**130 to 120 giga 0.85 to 0.8 LLNR**	**120 to 100 giga**	**< 100 giga**

		Grades		
Parameter	Origin	1	2	3
Platelets decrease (giga/L) assuming no platelet cluster	**CPI**	**130 to 120 giga**	**120 to 100 giga**	**< 100 giga**
	FDA	**140 to 125 giga**	**124 to 100 giga**	**99 to 25 giga**

Very similar

		Grades		
Parameter	Origin	1	2	3
Platelets decrease (giga/L) assuming no platelet cluster	**CPI**	**130 to 120 giga**	**120 to 100 giga**	**< 100 giga**
	FDA	**140 to 125 giga**	**124 to 100 giga**	**99 to 25 giga**
	NIH	**125 to 100 giga**	**99 to 50**	**49 to 25**

Too low values in NIH guideline…
…due to AIDS treatment specificities

The same process could be applied

on ECG/Vital signs

or on any finding …

Safety adaptation: Upgrading (2)

CPI suggest possible "**upgrading modulation**" *

1. Fast worsening
2. Association to other concomitant changes
3. Association to clinical signs or symptoms
4. Occurrence in several subjects

* FDA Draft guidance Oct 2007

Third part

Decision making process:

the « stopping rules »

CPI proposals

3. *Decision making process Stopping rules*

- Difficulty due to usual conflict-of-interest :
  - Subject safety (and protection) → caution
  - Learning on drug → pushing dose escalation
- Therefore …stopping rules are required

Stopping rules
CPI proposal

Individual *level*

Any event of grade equal or greater than 3

→ stopping that subject

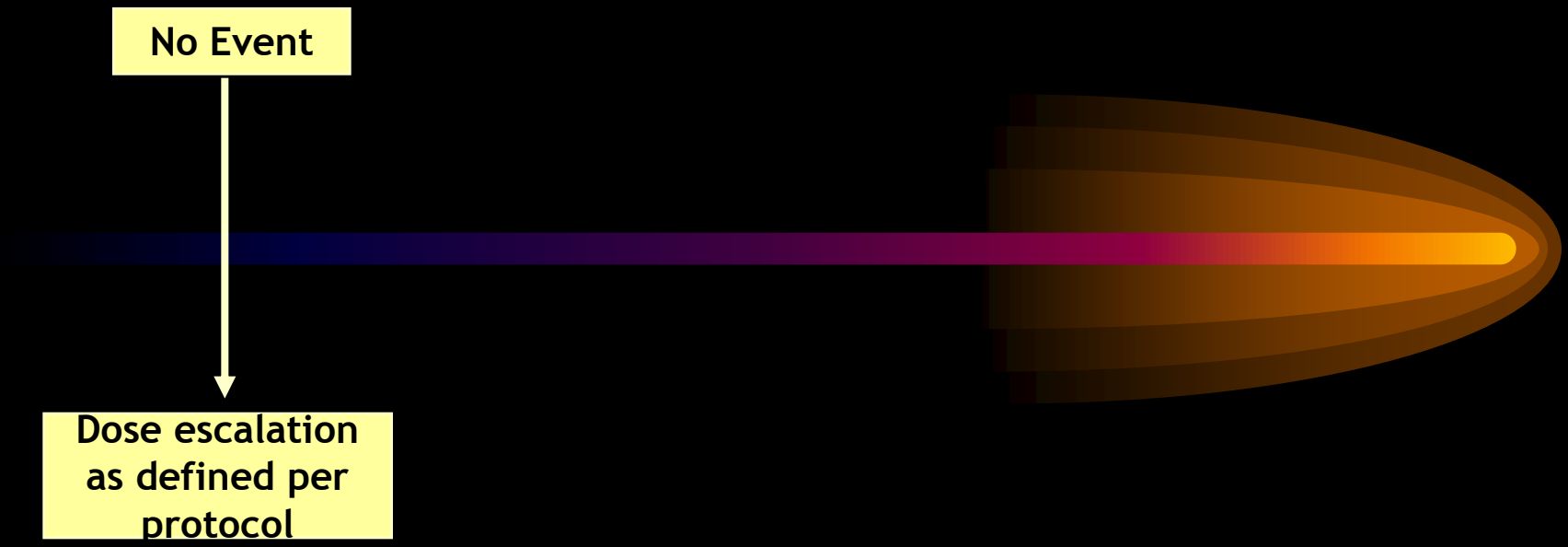
(or grade 2 modulation to upgrading)

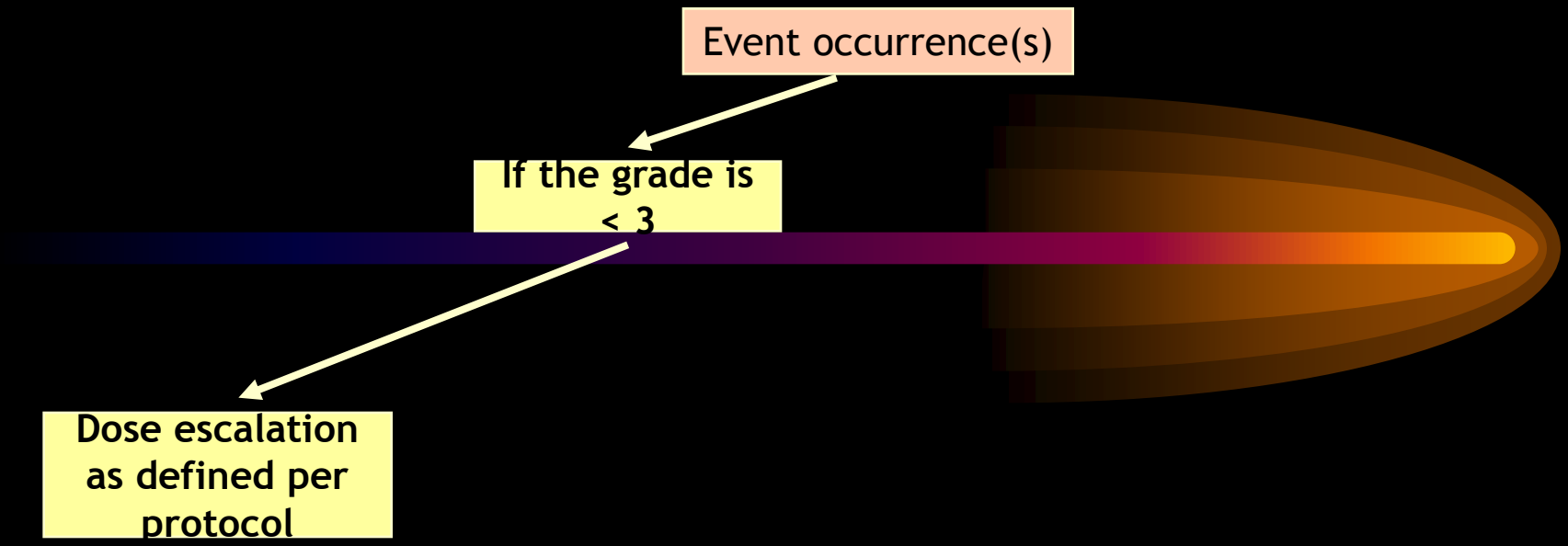
Cohort *level*

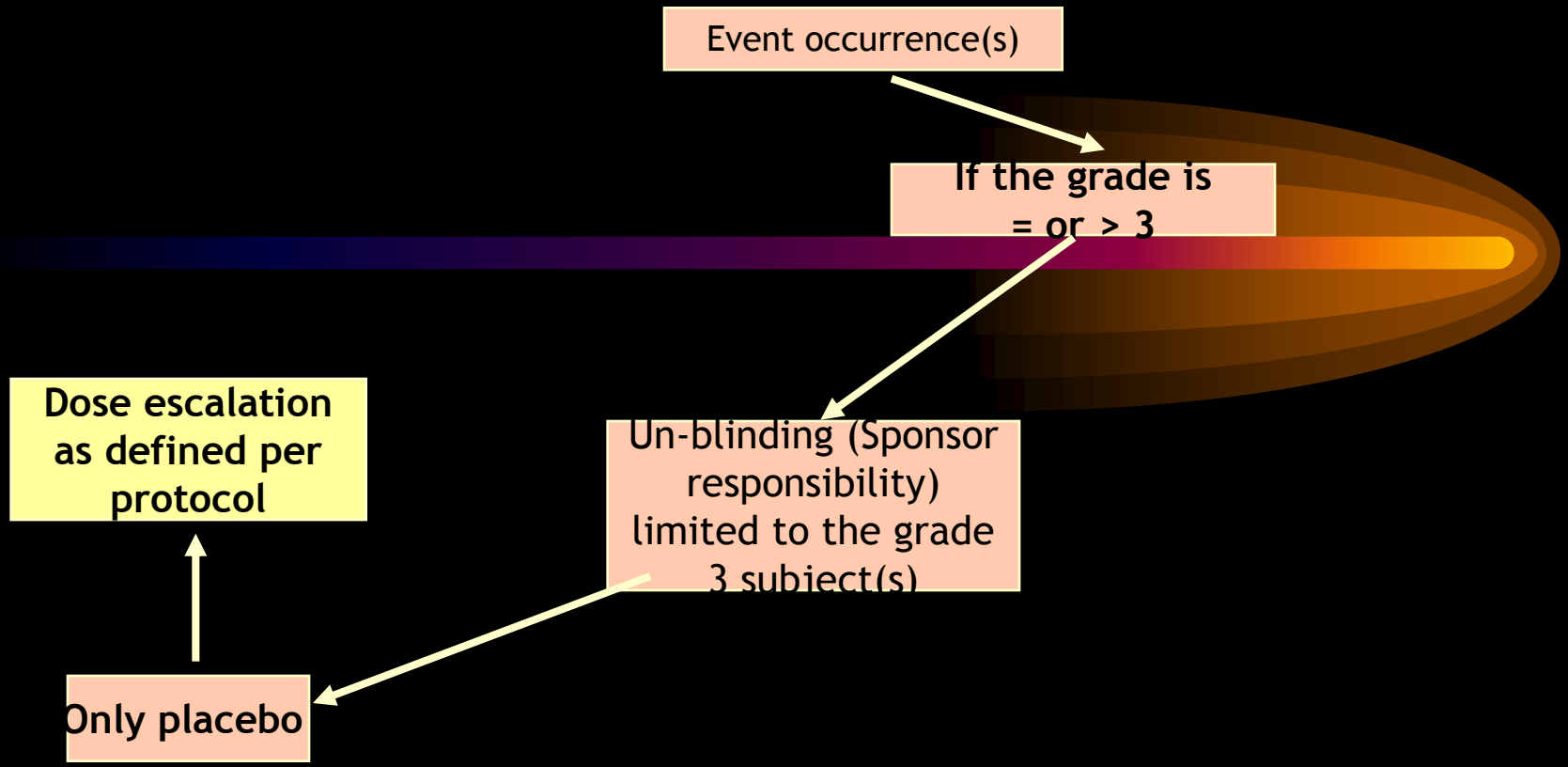
Decision based on:

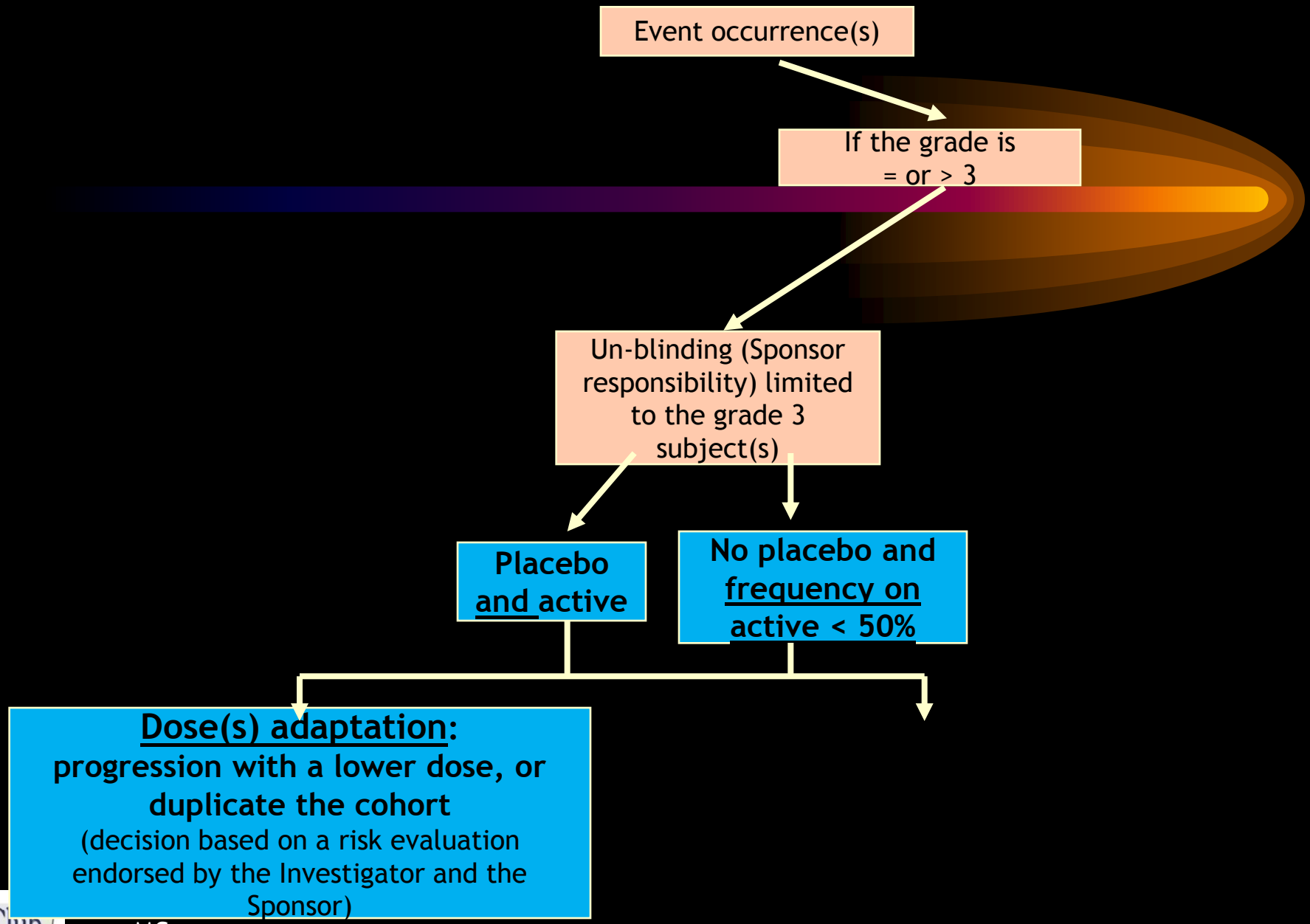
- Intensity of events
- Number/fequency of events
- Placebo or active

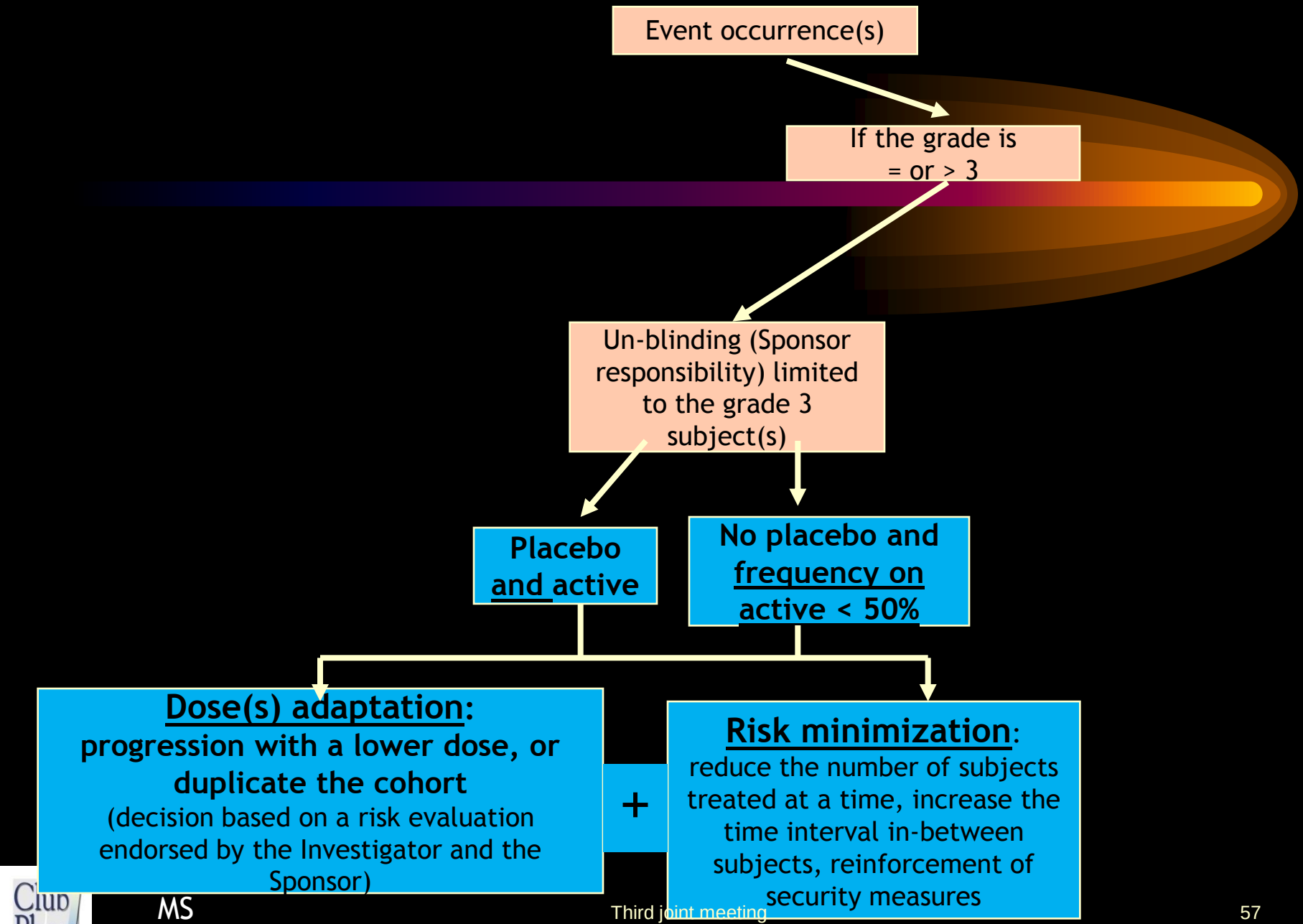
→ proposed CPI algorithm

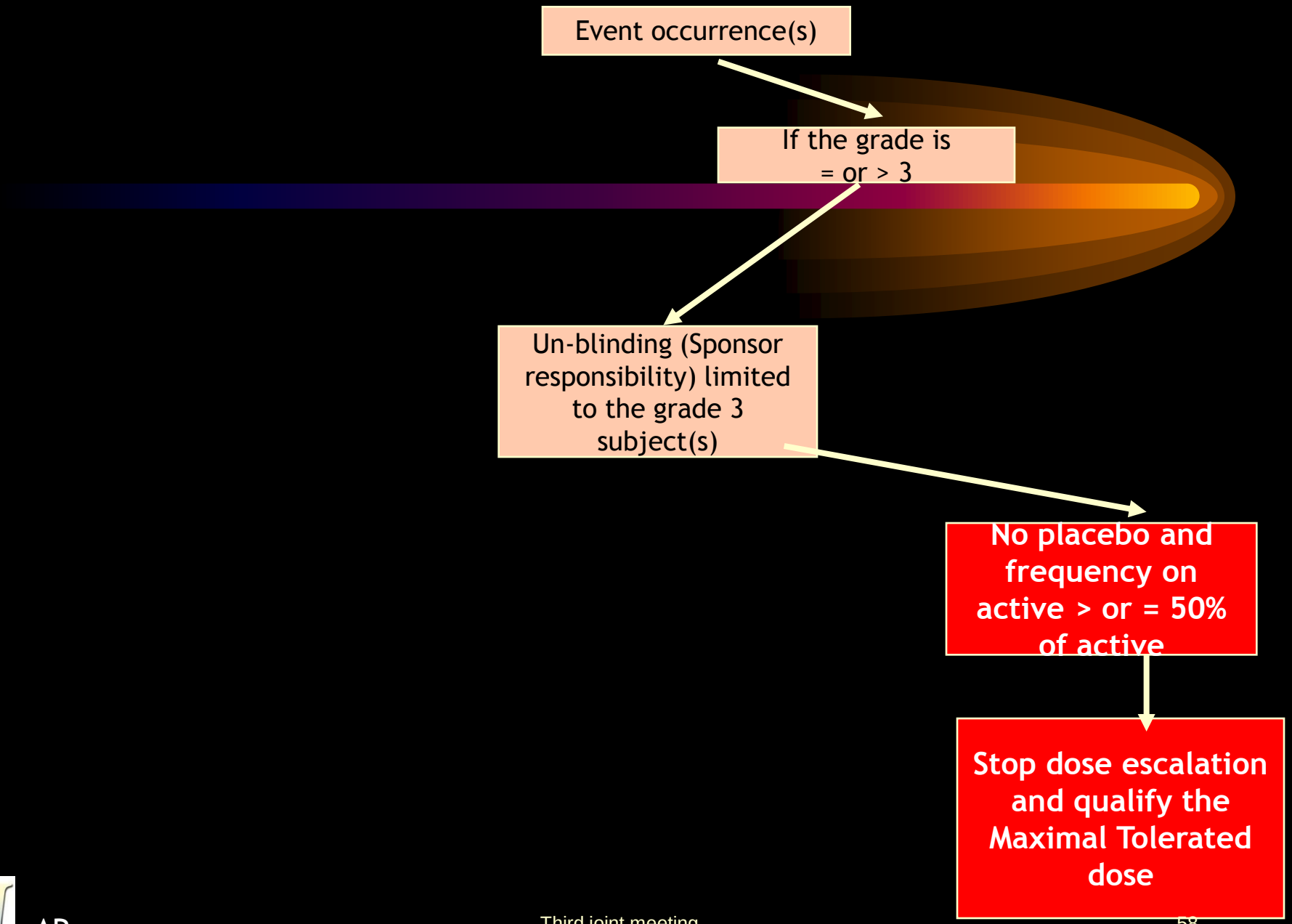

No Event
Dose escalation as defined per protocol

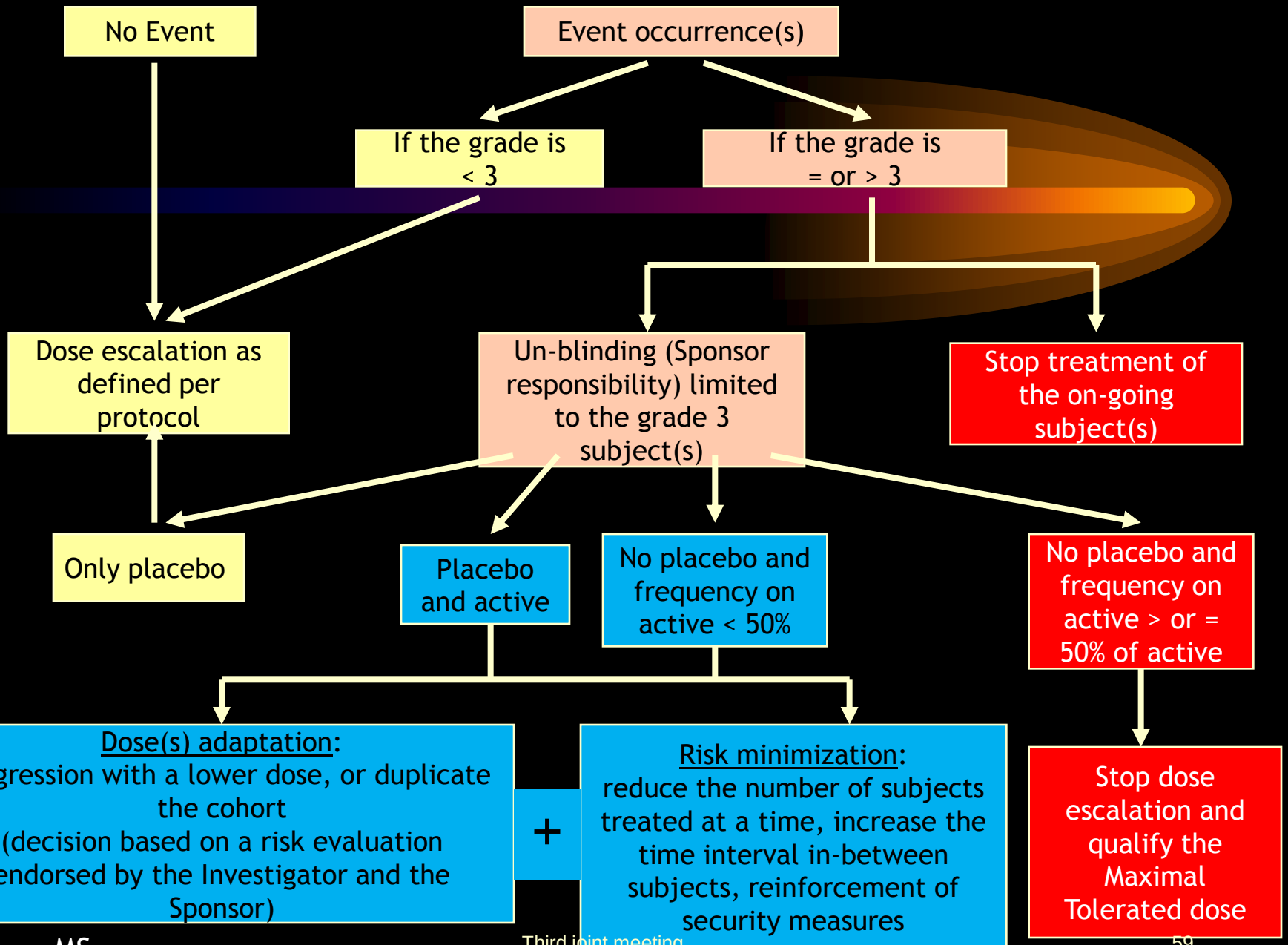

Event occurrence(s)
If the grade is < 3
Dose escalation as defined per protocol


Event occurrence(s)
If the grade is = or > 3
Un-blinding (Sponsor responsibility) limited to the grade 3 subject(s)
Only placebo
Dose escalation as defined per protocol


Event occurrence(s)
If the grade is = or > 3
Un-blinding (Sponsor responsibility) limited to the grade 3 subject(s)
Placebo and active
No placebo and frequency on active < 50%
Dose(s) adaptation:
progression with a lower dose, or duplicate the cohort
(decision based on a risk evaluation endorsed by the Investigator and the Sponsor)


Event occurrence(s)
If the grade is = or > 3
Un-blinding (Sponsor responsibility) limited to the grade 3 subject(s)
Placebo and active
No placebo and frequency on active < 50%
Dose(s) adaptation:
progression with a lower dose, or duplicate the cohort
(decision based on a risk evaluation endorsed by the Investigator and the Sponsor)
+
Risk minimization:
reduce the number of subjects treated at a time, increase the time interval in-between subjects, reinforcement of security measures


Event occurrence(s)
If the grade is = or > 3
Un-blinding (Sponsor responsibility) limited to the grade 3 subject(s)
No placebo and frequency on active > or = 50% of active
Stop dose escalation and qualify the Maximal Tolerated dose


No Event
Event occurrence(s)
If the grade is < 3
If the grade is = or > 3
Dose escalation as defined per protocol
Un-blinding (Sponsor responsibility) limited to the grade 3 subject(s)
Stop treatment of the on-going subject(s)
Only placebo
Placebo and active
No placebo and frequency on active < 50%
No placebo and frequency on active > or = 50% of active
Dose(s) adaptation: progression with a lower dose, or duplicate the cohort (decision based on a risk evaluation endorsed by the Investigator and the Sponsor)
+
Risk minimization: reduce the number of subjects treated at a time, increase the time interval in-between subjects, reinforcement of security measures
Stop dose escalation and qualify the Maximal Tolerated dose

Conclusions

1. Points to consider, but not guideline
2. Improved proposals, due to accurate bases & methods
3. Fit to healthy subject and all types of FIMs
4. Adapt if PD objective (ie. aPTT anticoagulant) ; those tresholds are not dedicated as limit for screening
5. “Suggestions” but decision upon investigator responsibility

The 

working party…

…thank you for your attention !

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