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Issues in reporting statistical results of safety pharmacology studies according to new guidance

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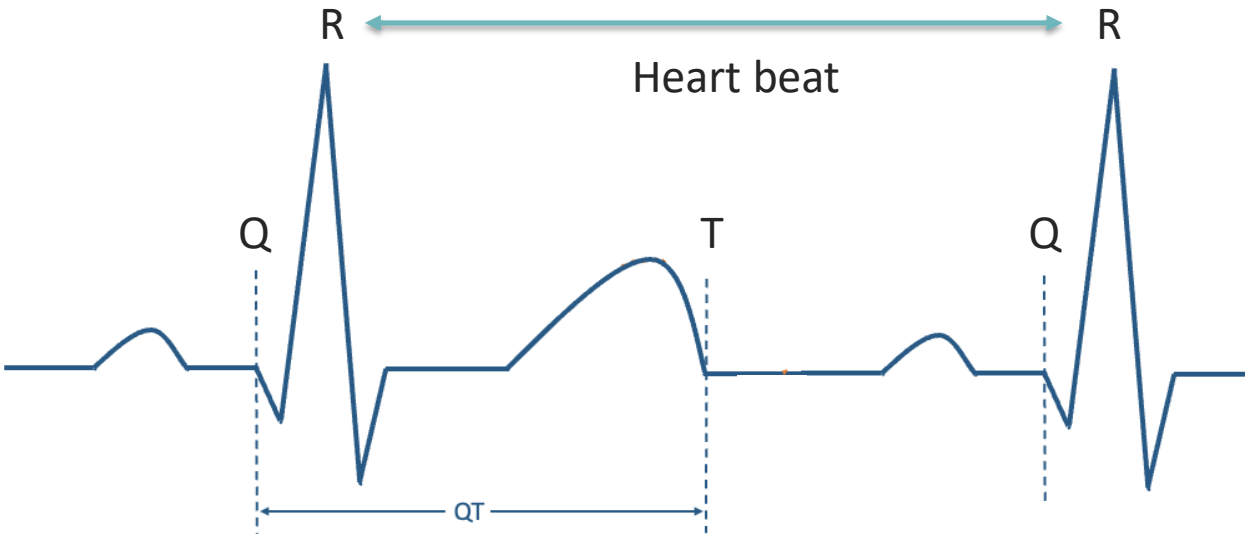
Non-Clinical Statistics Conference 2024, Wiesbaden, Germany, Sept. 25-27

Safety pharmacology parameter of concern is

QT-interval, in ms —getting rid of the HR dependency→ QTc-interval (corrected QT), in ms



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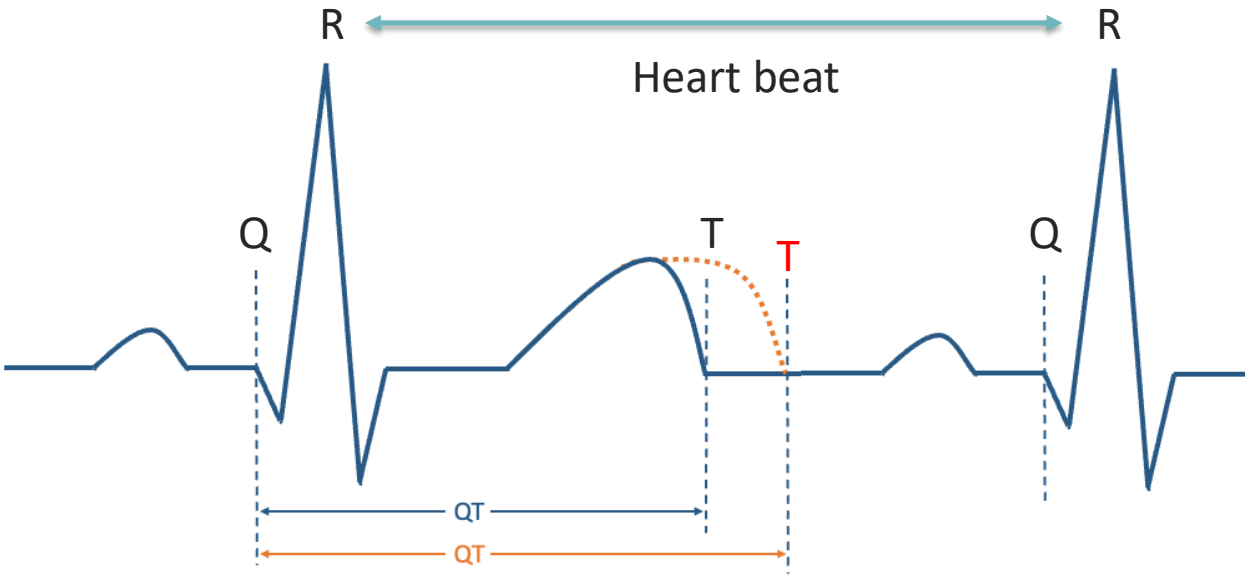

Typical Experimental Design in Safety Pharmacology

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Crossover 4X4 Latin Square Design

4 Dogs

4 Treatments:
V – Vehicle
LD – low dose
MD – mid dose
HD – high dose

4 Treatment Periods

	Treatment Period I	Treatment Period II	Treatment Period III	Treatment Period IV
Dog 1	LD	HD	MD	V
Dog 2	V	MD	LD	HD
Dog 3	HD	LD	V	MD
Dog 4	MD	V	HD	LD

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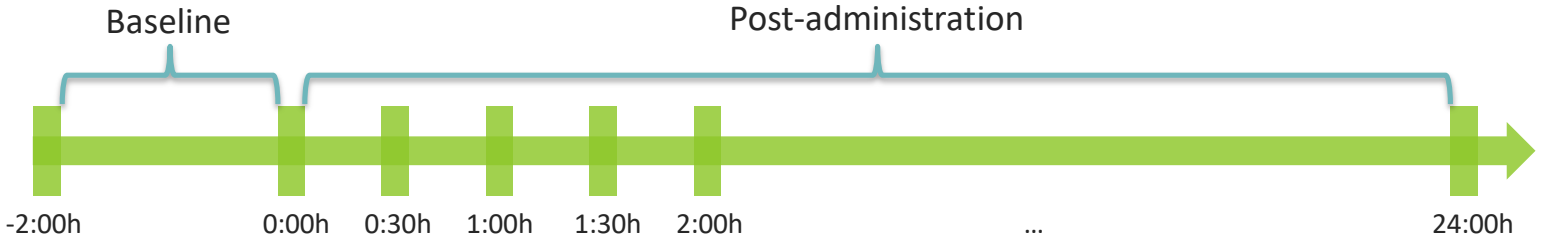
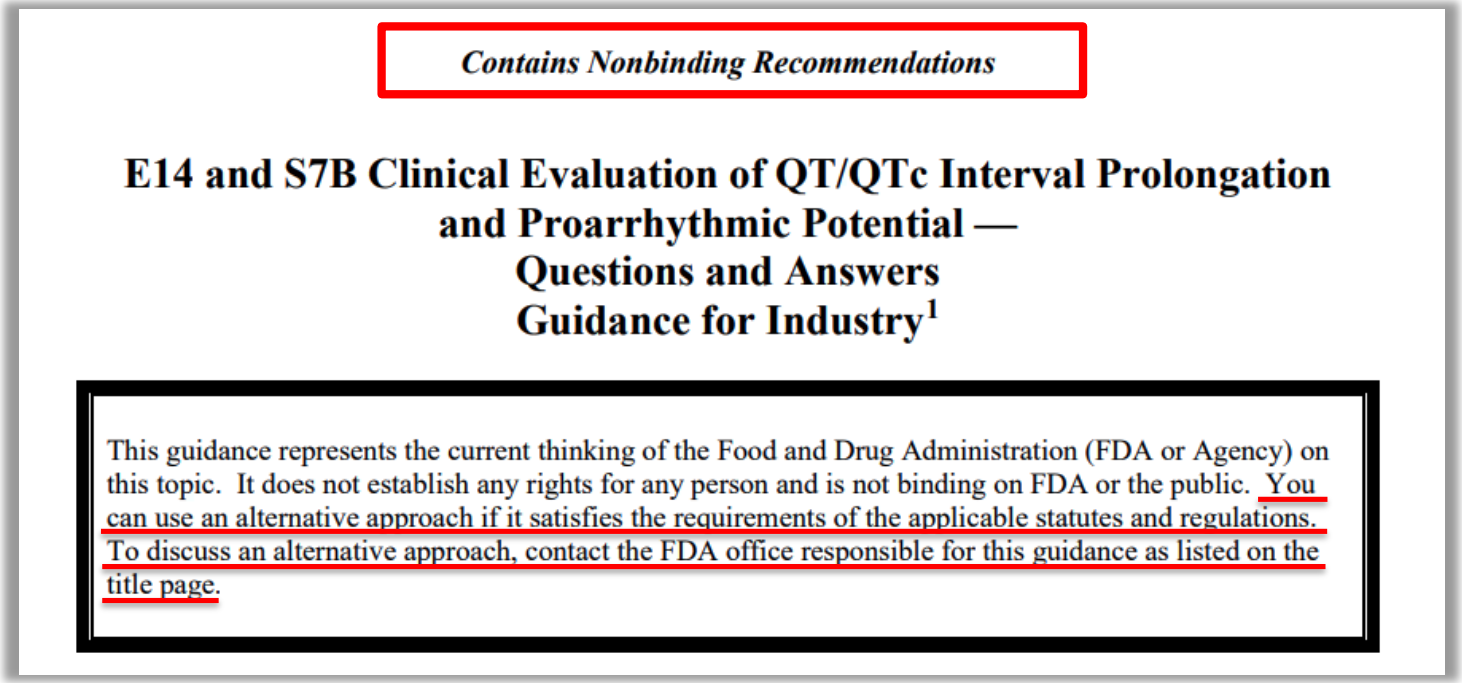
Each Dog at each Treatment Period:



New guidance (08/2022)



Contains Nonbinding Recommendations

E14 and S7B Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential — Questions and Answers Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

New guidance (08/2022)

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Table 1-D. In Vivo QT Assessment

QT Study	
Exposure	The 10 mg/kg dose provides a 2-fold margin over high clinical exposures
Design[1]	*Crossover, N=4*
Species:	*Dogs*
Historical QTcI Sensitivity:	*MDD: 8 ms (95% CI: 6 ,10)*
ECG collection	*24-h telemetry*
ECG reading methodology	*Fully automated*
PK Collection	*Same study, at 3 h post-dose* *Cmax characterized at same dose levels in Toxicokinetic Study*
Analysis Methods:	
Data reduction method	*0-3 h, 3-8 h, 8-12 h, 12-18 h, 20-24h after dosing (super-intervals)*
Analysis methodology	*By-time window using ANOVA*
HR correction method	*QTcI based on 24 h baseline data in each animal*
ECG Findings	*No ventricular tachyarrhythmias*

Summary Findings

Moiety & Dose	*QTcI Effect Size (ms ± SE)[2]*	*Parent concentration at 3 h (ng/mL)[3]*	*C_{max}-total (ng/mL)[4]*	*C_{max}-free (ng/mL)[5]*	*Protein Binding: Species (%)[6]*	*High Clinical $C_{max,ss}$ (ng/mL)[7]*	*Exposure Ratio[8]*
0.5 mg/kg	1 ± 4	7	10	10	1% (dog) 1% (human)	*291 (95% CI: 265 – 319)*	0.03
3 mg/kg	-3 ± 5	55	60	59			0.2
10 mg/kg	2 ± 3	595	582	576			2.0
MDD[9]	10 ms						

Source: ICH E14/S7B Q&As Training Material Examples Supplemental File

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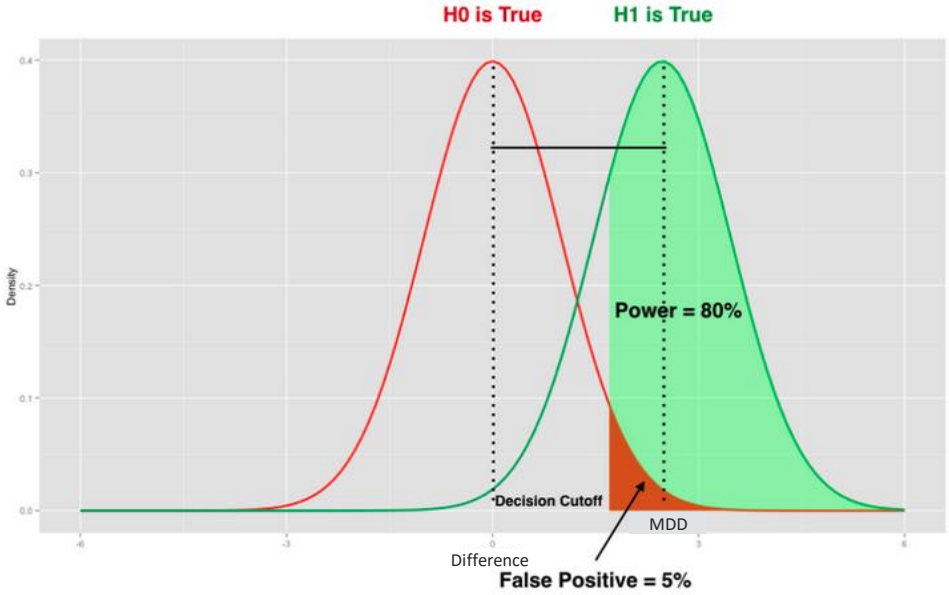
„Best practice considerations for nonclinical in vivo cardiovascular telemetry studies in non-rodent species: Delivering high quality QTc data to support ICH E14/S7B Q&As“

Historical QTc Sensitivity → Historical Power Analysis

I. Based on the cohort of historical studies (15-30) → What to do if less than 15 studies conducted?

Historical QTc Sensitivity → Historical Power Analysis

MDD is the smallest difference between the means of the treatment and control groups that can be statistically significant (**with 80% power**).



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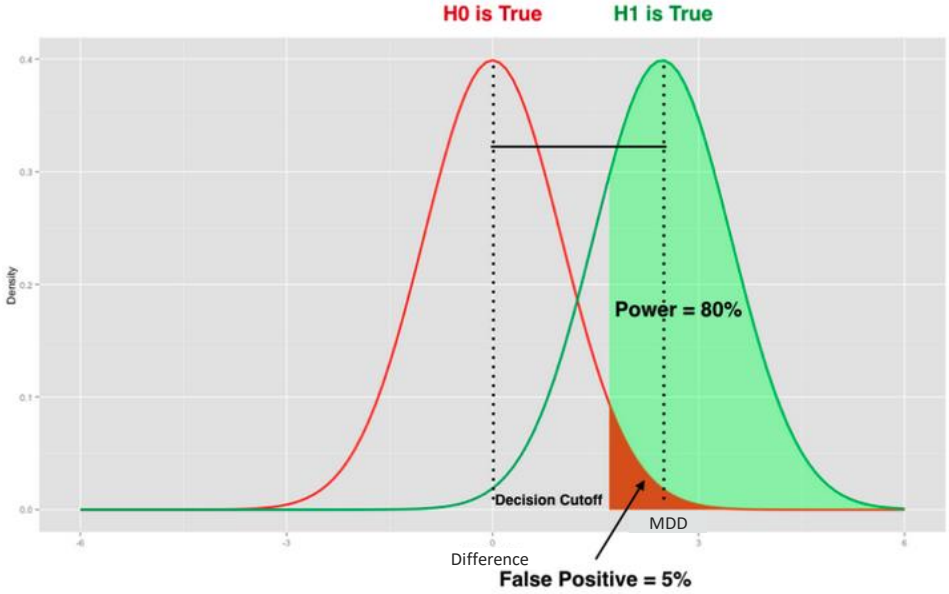
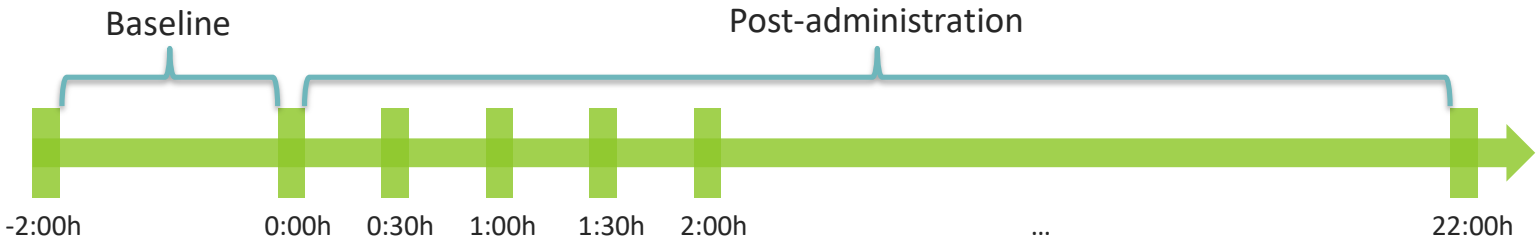


Between which treatment groups?

At which time point?

Historical QTc Sensitivity → Historical Power Analysis

II. Data reduction method. Super-intervals can be built. → How are the super-intervals to be chosen?



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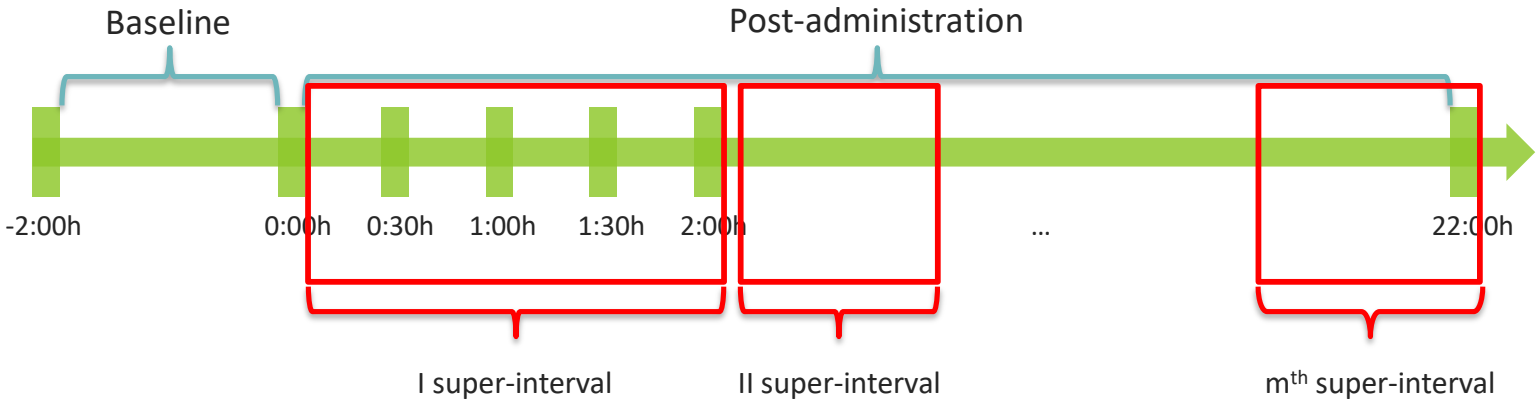

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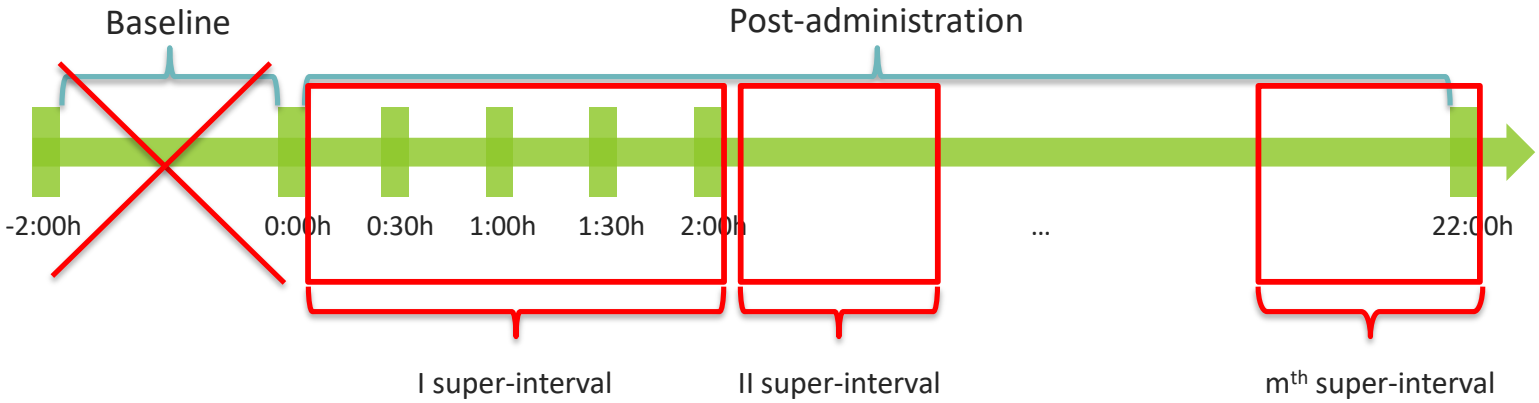

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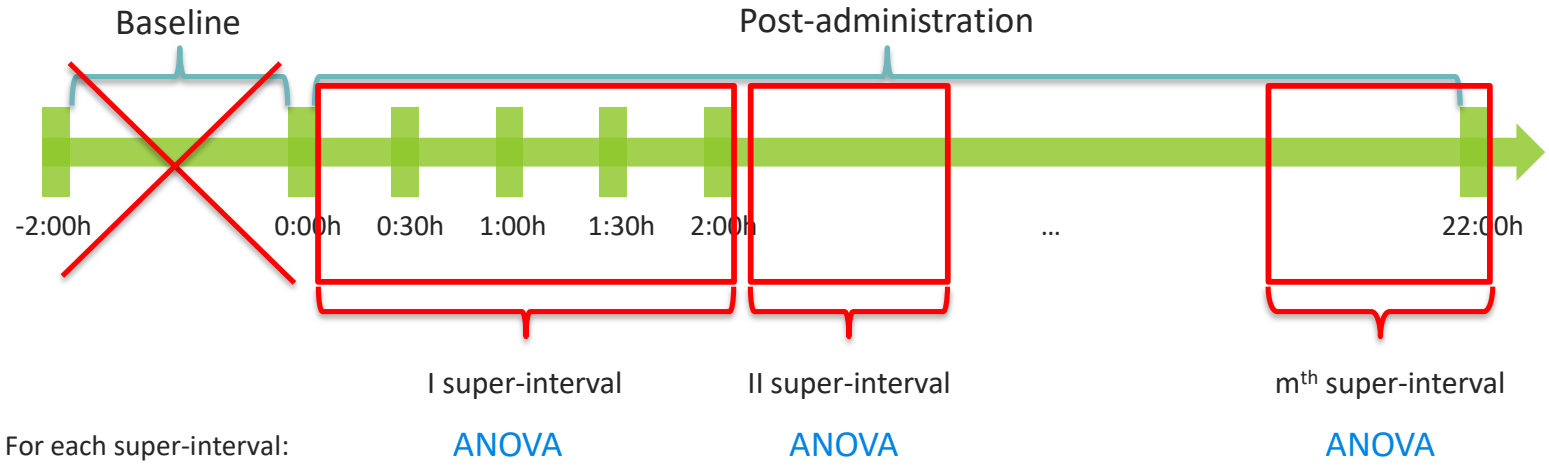
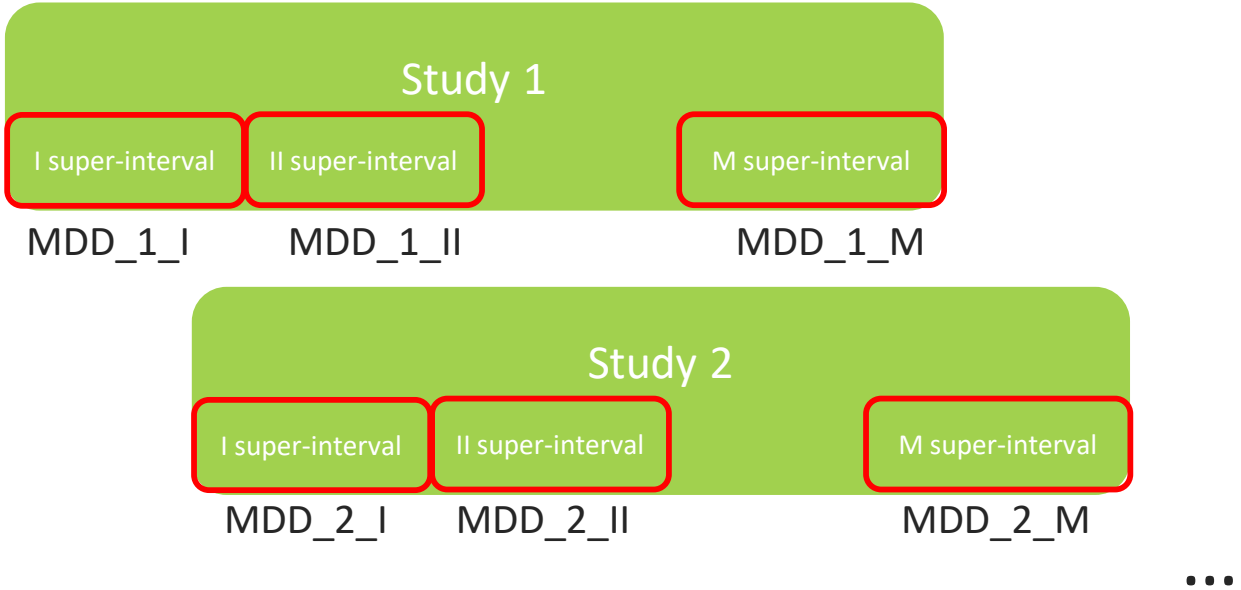


ANOVA: Post-administration ~ Dog + Treatment + Treatment Period

Historical QTc Sensitivity → Historical Power Analysis

MDD is computed for each super-interval in each historical study.



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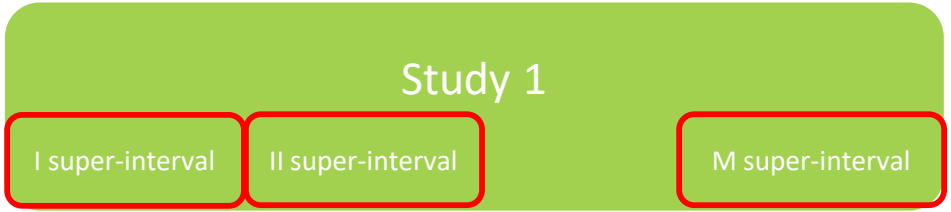
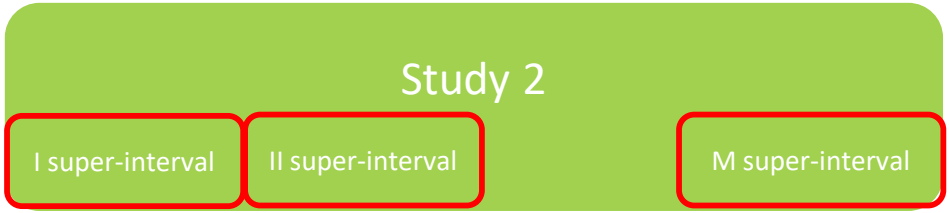


MDD_1_I MDD_1_II MDD_1_M → MDD_1:=median(MDD_1_I,…, MDD_1_M)



MDD_2_I MDD_2_II MDD_2_M → MDD_2:=median(MDD_2_I,…, MDD_2_M)

…

MDD of the study is the median of MDDs for super-intervals in this study.

Historical QTc Sensitivity → Historical Power Analysis

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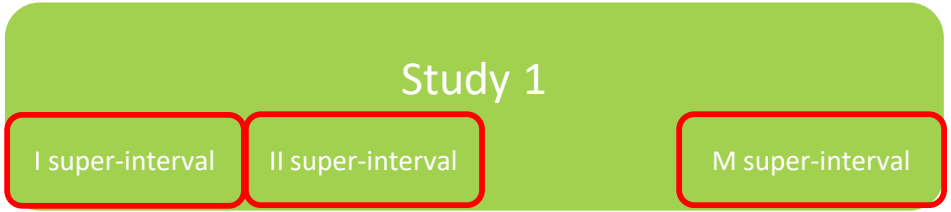

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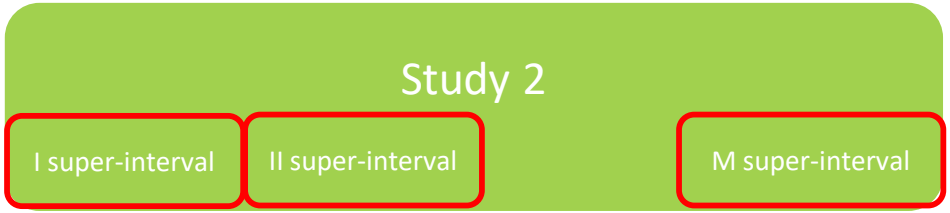

MDD_2_I MDD_2_II MDD_2_M → MDD_2:=median(MDD_2_I,…, MDD_2_M)

…

Historical MDD is the median of the MDDs for the studies: MDD:=median(MDD_1,MDD_2,…,MDD_N)

III. Historical MDD for the built super-intervals represents the median MDD for the averaged values

→ How helpful is it for the determination of the QTc prolongation?

IV. „Historical MDD should be less than 10 ms“

→ Safety pharmacologists feel obliged/demand to build a statistical methodology that delivers MDD less than 10ms

Summary

I. Results of the historical power analysis heavily depend on the applied statistical methodology

II. Safety pharmacologists feel pressure from the authorities and want to obtain the historical MDD under 10 ms by any means

III. Nevertheless, the chosen statistical methodology should satisfy needs of the biological interpretation

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Thank you for your attention!

(any questions, concerns, comments, advices?)