Imaging in Osteoarthritis Clinical Trials: Metrics and endpoints Medical Imaging

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Agenda

- *Uses of Medical Imaging*
- *Imaging Requirements*
  - *The metrics of measurements*
- *Conclusions*

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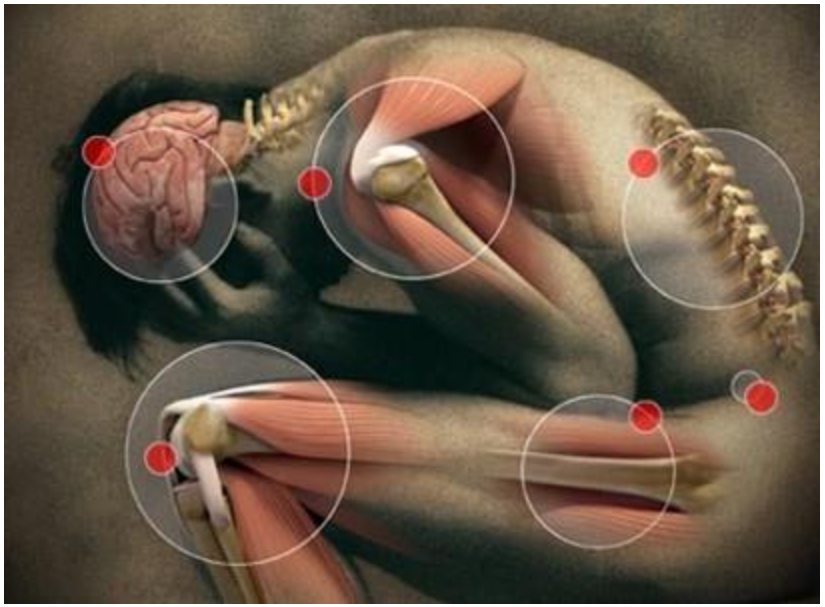
Uses of Medical Imaging

- *Diagnosis*
- *Prognosis*
- *Monitoring therapy*
- *Monitoring Natural History of Disease*



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Imaging Requirements

- ***Diagnostic Sensitivity***
- ***Precision/Accuracy***
- ***Reliability***
- ***Relevance***
- ***Cost effective***
- ***Acceptance by regulatory agencies***
- ***Acceptability to Subject***
- ***Safety to subject and operator***

Bone density measurements in clinical trials: the challenge of ensuring optimal data;
Miller CG, Br. J Clin Res. 1993 Vol. 4, p. 113-120

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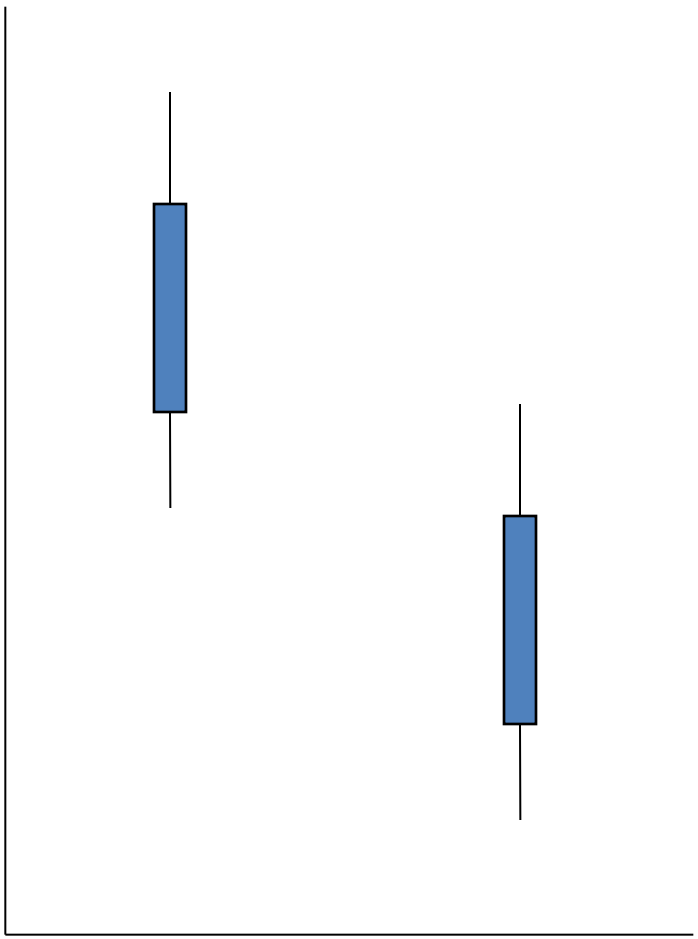
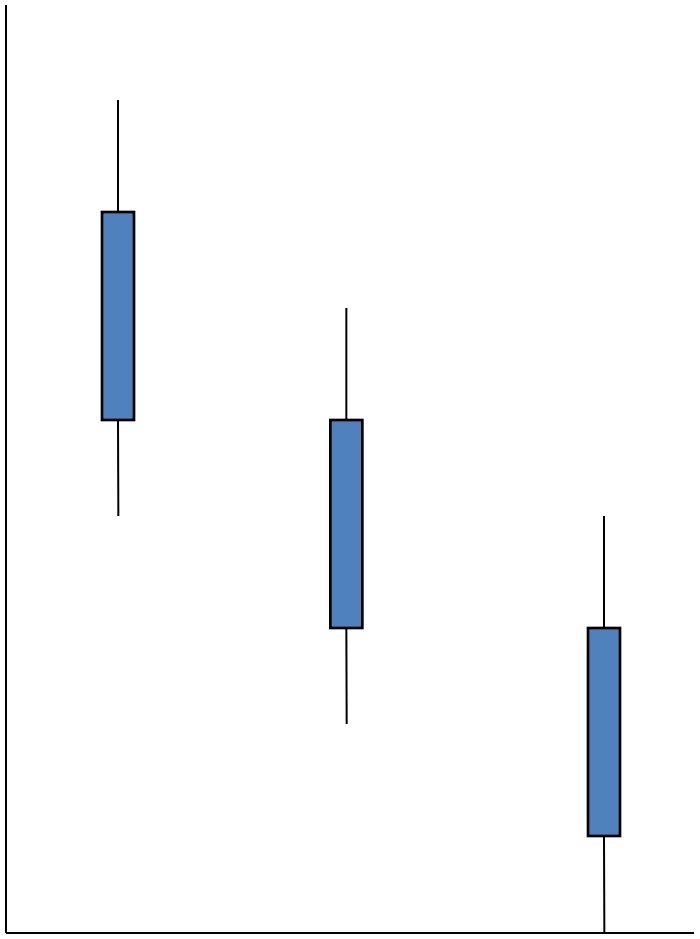
Diagnostic Sensitivity

Normal - Abnormal Difference



Normal Diseased



Normal Elderly Diseased

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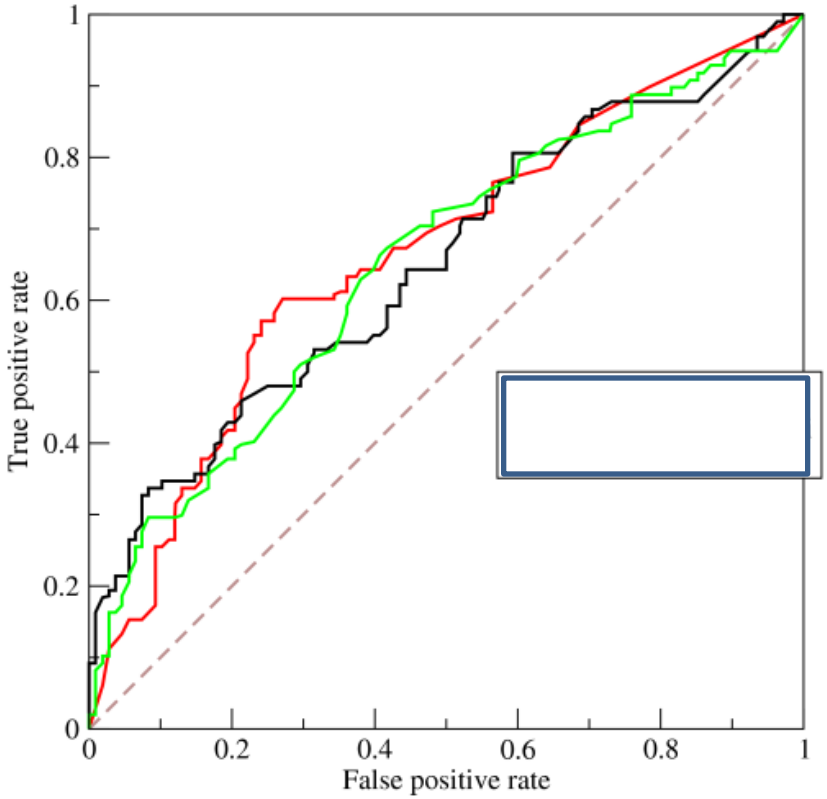
ROC Analysis

- *Sensitivity - True Positive*
- *Specificity – False positive*

Predicted Outcome

Actual Value

True +ve	False +ve
False -ve	True -ve



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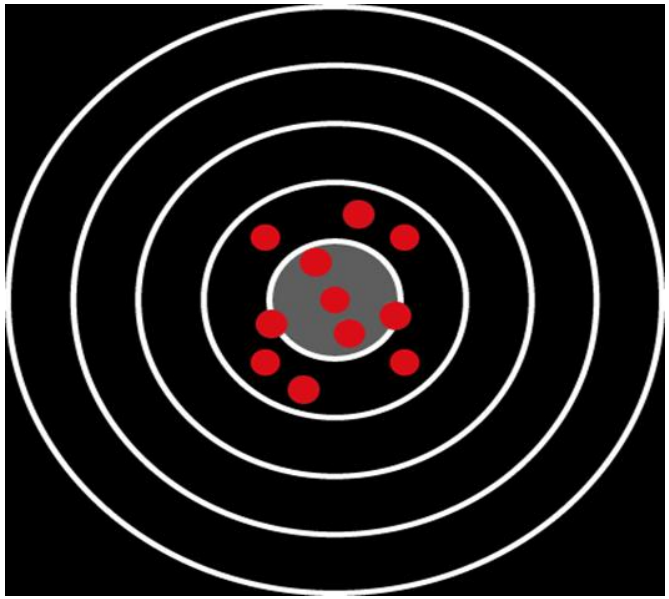
Accuracy



Standard error of the estimate of linear regression between actual and measured parameter

i.e., when correctly calibrated, the measured result is close to the actual value

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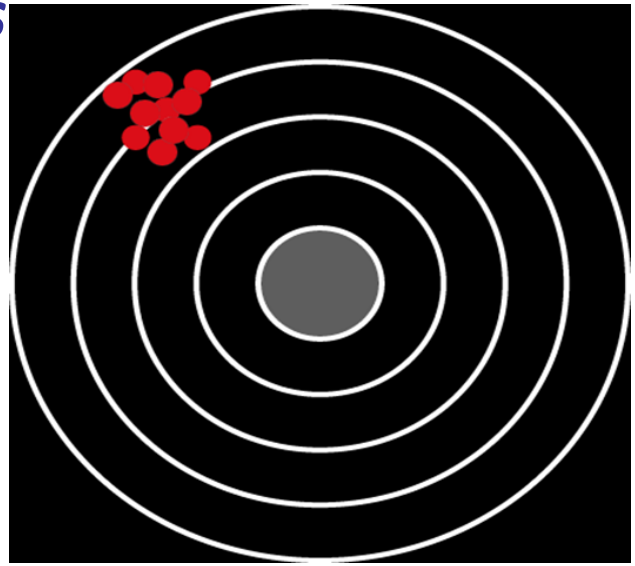
Precision

Standard deviation of the difference between pairs of repeat measurements, usually expressed as a percentage of the average value (coefficient of variation)

i.e., the reproducibility of the measurement. When repeating a measurement of the same object under the same circumstances, how similar are the results?



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Precision

Measured as coefficient of variation:

$$\%C.V. = \frac{S.D.}{Mean}$$

Standardized Coefficient of Variation:

$$S.C.V. = \frac{S.D.}{Mean} \times \frac{Mean}{Normal\ Range} = \frac{S.D.}{Normal\ Range}$$

NB: Normal range = 5%-95%

MillerCG et al Osteo Int 1993

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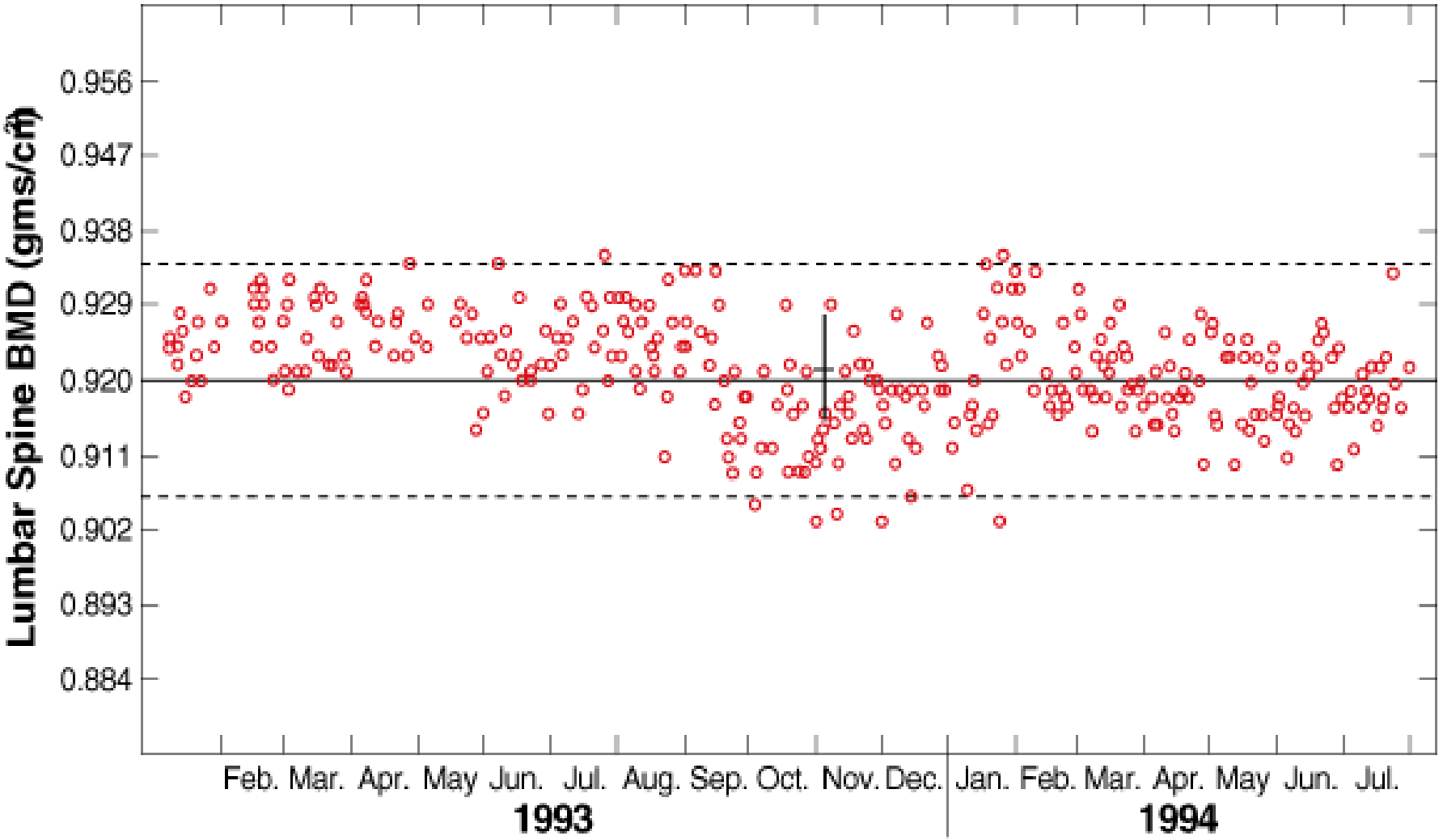
One Problem – Calibration drift



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Reliability – Site Selection

- *Subject recruitment*
- *Imaging Modalities*
  - *X-ray – How to standardize?*
  - *MRI 1.5T or 3.0T?*
- *Trained technologists?*
  - *Open to being trained?*
  - *Accept trial standard – not local site standard?*
- *Imaging Guidelines*

Reliability – Image QC

- *Training*
  - *Sites – good acquisition*
  - *Central Readers (radiologists)*
- *Administrative QC*
  - *Anonymized*
  - *Right subject, right time point?*
- *Image QC*
  - *Correct anatomical coverage?*
  - *Motion artifacts?*
  - *Acquired according to Imaging Guidelines?*
- ***Up to 30% of all images will be poor quality or unusable without Image QC***

Reader Reliability

- *Qualified Radiologists*
- *Reader training on the read scoring system*
  - *EG KL or Modified KL (at least 10 versions)*
  - *How to score WORMS, BLOKS, MOCART etc*
- *Inter-reader calibration*
  - *Eligibility*
  - *Efficacy/Safety*
- *Inter and intra Reader calibration*
  - *on going?*

Reliability – Computer systems

- *Validation*
- *CFR 21 Part II compliance*
  - *Image Management systems*
  - *Read systems*
- *Meets new FDA draft Guidance for Industry:*
  - *Guidance for Industry: Standards for Clinical Trial Imaging Endpoints (Aug 2011)*
  - *EG Charter, monitors, phantoms, QC etc*

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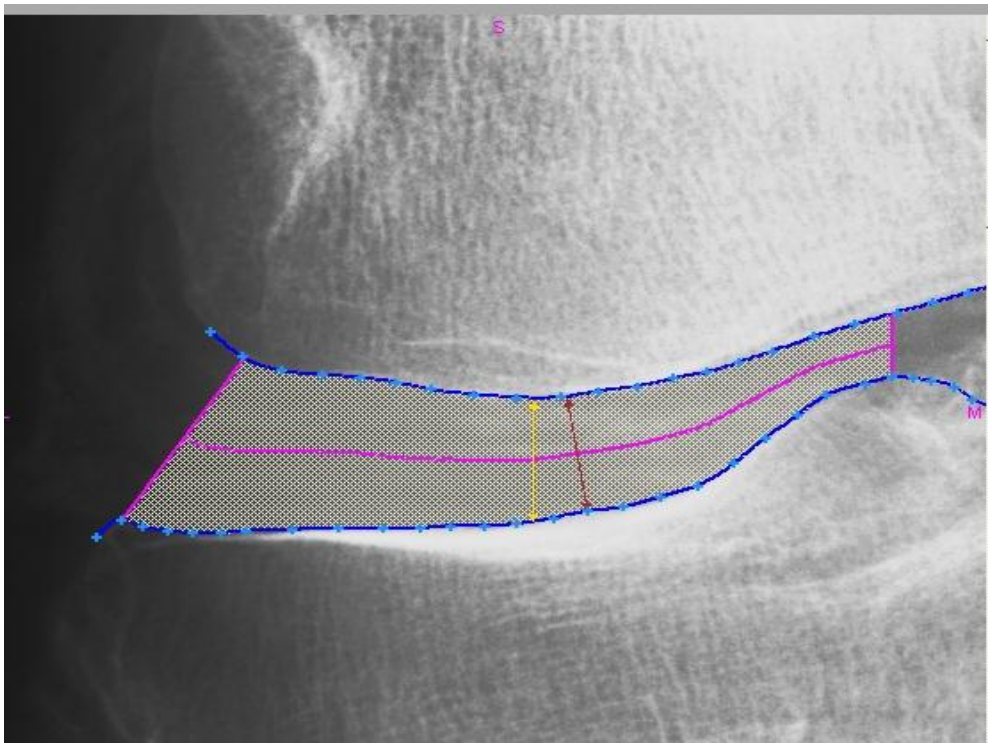
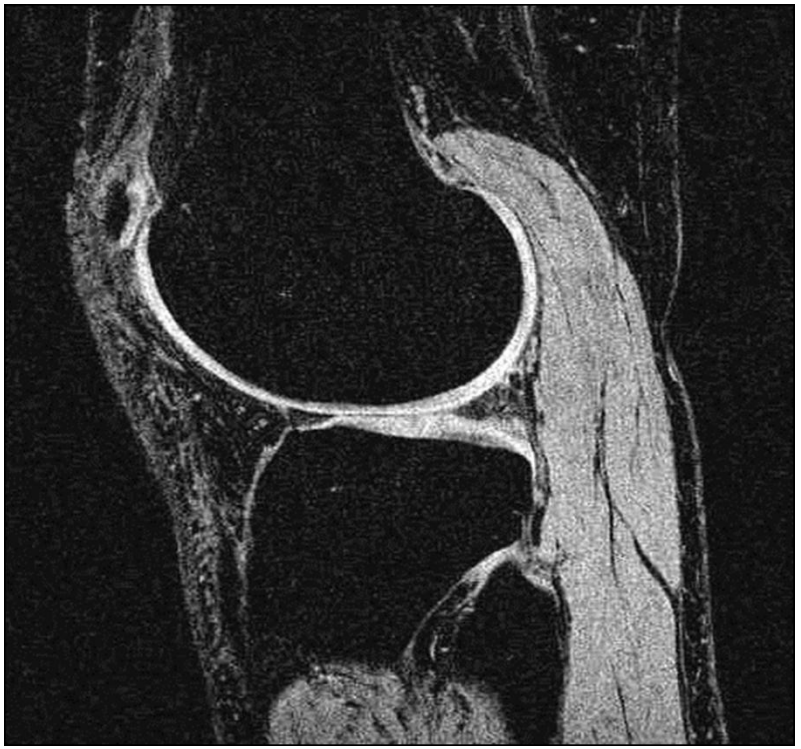
Gold Standard?



Or Best method?



Do either have any clinical meaning or relevance?

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Validation

- *Validation as a BioMarker/Surrogate*
- *Does this match the requirements for a biomarker/surrogate end point?*
- *Is it on the correct biological pathway?*

Validation

- ***Validation as a BioMarker/Surrogate***
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- ***Is it on the correct biological pathway?***

BioMarker Definitions

"A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results."

A probable valid biomarker is defined as

"a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results."

FDA *Guidance for industry—pharmacogenomic data submissions 2006*

Validation

- *Validation as a BioMarker/Surrogate*
- *Does this match the requirements for a biomarker/surrogate end point?*
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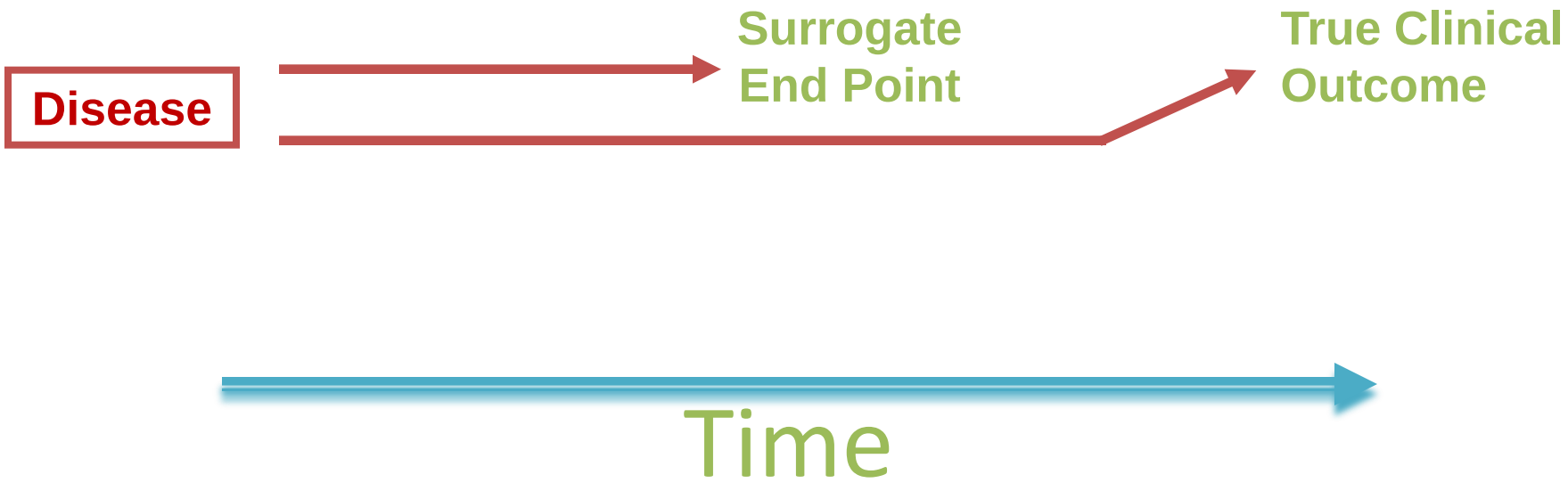
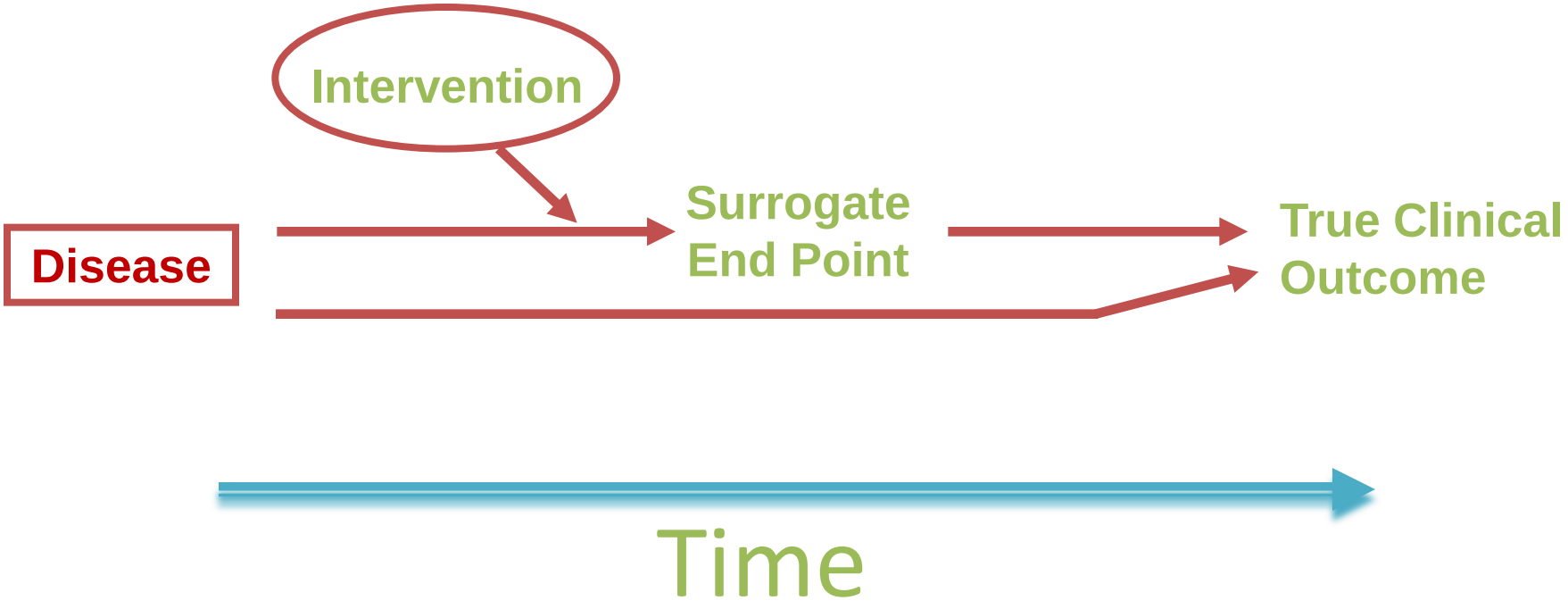
Reasons for Surrogate Failure: 1



Reason for failure of surrogate end point:
The surrogate is not in the causal pathway of the disease process.

Fleming TR, DeMets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Annals of Int Med; 125; 605-613, 1996***d.*** 1996:125:605-613

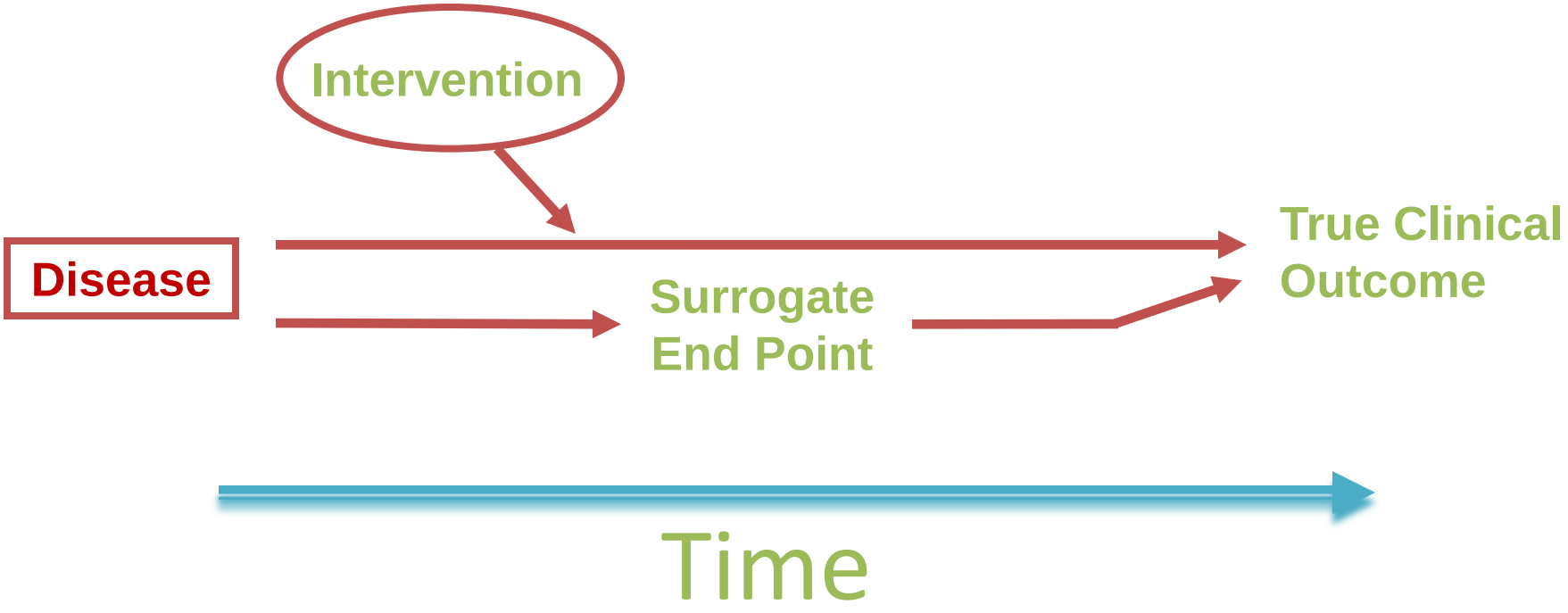
Reasons for Surrogate Failure: 2



Reason for failure of surrogate end point:
Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate.

Fleming TR, DeMets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Annals of Int Med; 125; 605-613, 1996***d.*** 1996:125:605-613

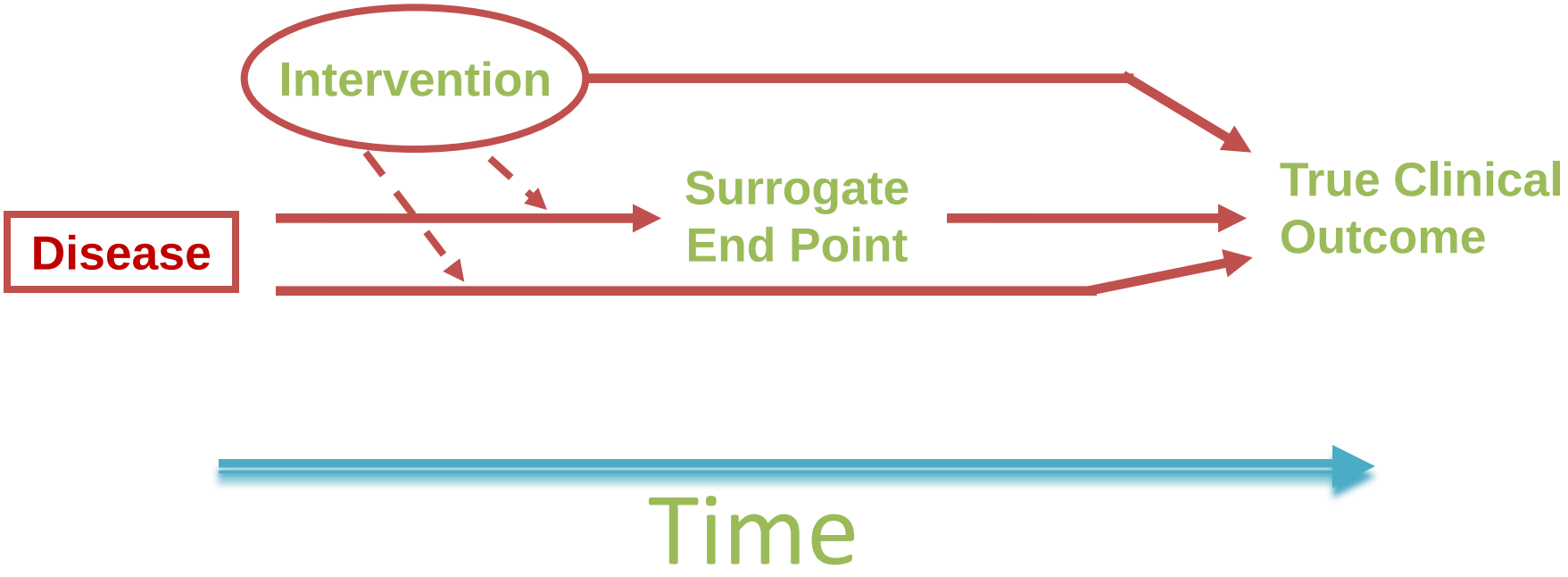
Reasons for Surrogate Failure: 3



Reason for failure of surrogate end point:
The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect.

Fleming TR, DeMets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Annals of Int Med; 125; 605-613, 1996***d.*** 1996:125:605-613

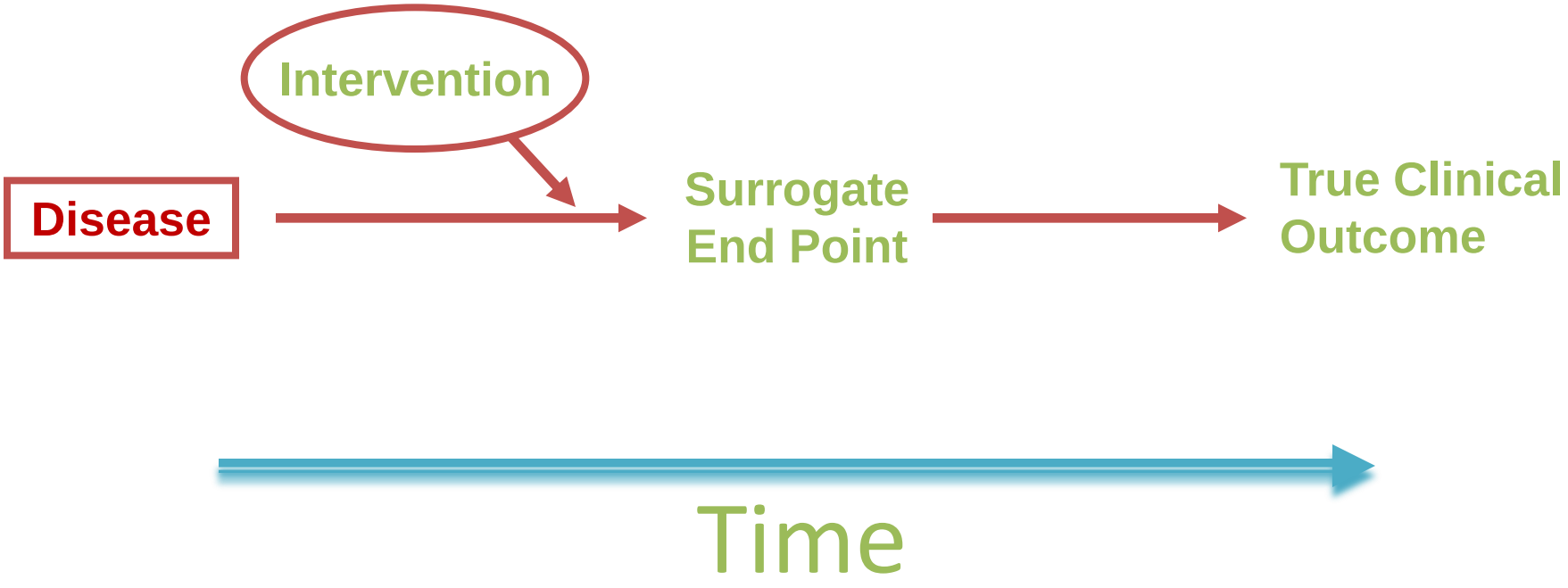
Reasons for Surrogate Failure: 4



Reason for failure of surrogate end point:
The intervention has mechanisms of action independent of the disease process.
Dotted lines = mechanisms of action that might exist.

Fleming TR, DeMets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Annals of Int Med; 125; 605-613, 1996***d.*** 1996:125:605-613

Reasons for Surrogate Success:



The setting that provides the greatest potential for the surrogate end point to be valid.

Fleming TR, DeMets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Annals of Int Med; 125; 605-613, 1996***d.*** 1996:125:605-613

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- *Patient acceptability*
- *Safety to patient and operator*

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Cost Effective

Varies with study phase

- ***Phase I/II - Not relevant***
- ***Phase III***
- ***Phase IIIb***
- ***Phase IV and clinical setting***

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Acceptable to Regulatory Agencies

- *For general use*
- *For special use cases*
- *Supporting data in clinical trial submissions*

E.G. MRI is an accepted clinical endpoint, but NOT clinical trial end point

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FDA Directives

- *March 1997*
  - *Guidance states that a single, multi-endpoint trial may be used in lieu of several separate trials. Example: Betaseron*
- *October 1998*
  - *Draft Guidance for Industry - Developing Medical Imaging Drugs and Biologics.*
- *June 2004*
  - *Guidance for industry Developing Medical Imaging Drug and Biological Products, Part 1, Part 2, Part 3.*
- *October 2011*
  - *Draft Guidance for Industry on Standards for Clinical Trial Imaging Endpoints*
- *Expected final Oct/Nov 2012*
- http://www.regulations.gov/#!searchResults;rpp=10;po=0;s=FDA%25E2%2580%25932011%25E2%2580%2593D%25E2%2580%25930586

Regulatory Issues

- *Image data will be treated with the rigor as other clinical data*
  - *Loss of data viewed seriously*
  - *95% image data submission is possible*
- *Site Image Acquisition*

- *Efficacy Assessment*
  - *Independent*
  - *Central*
  - *Blinded Readings*
- *End point data should match the protocol end point (not always the case!)*

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Regulatory Issues

- ***Standardized Reading Process***
  - ***Identical Hardware/Software***
  - ***Same image display order of randomized images***
  - ***Allow for 100% duplication of reading process***

- ***Optimum Method to Display Images***
  - ***Digital Images***
  - ***Electronic control of data retrieval***
  - ***Digital measurements***
  - ***Reproduce image display order***
  - ***Review response assessments***

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Subject Acceptability

- *Is it comfortable*
- *Is it frightening?*
- *Is it a +ve experience?*
  - *EG MRI – Claustrophobia*
- *How does the technologist treat the subject?*
- ***Will the subject return for follow-up?***

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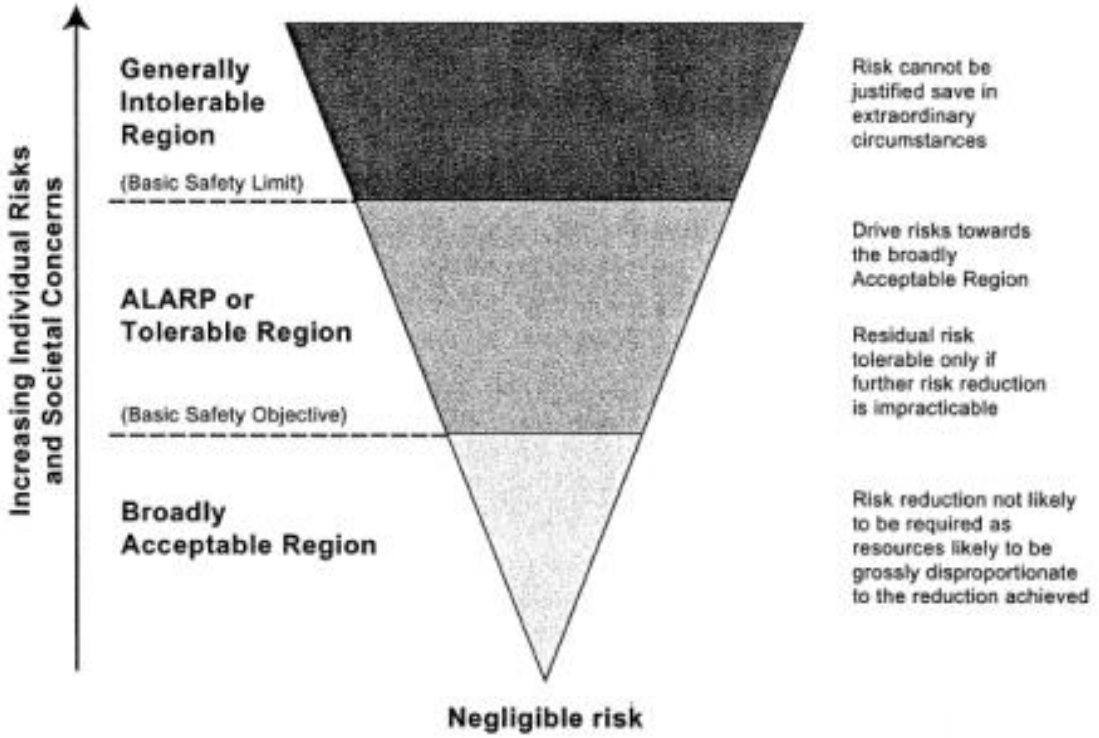
Safe for the Subject



Variable levels of risk depending on

- *Phase of study*
- *Disease*
- *Phase of the disease*

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Safety for the Operator

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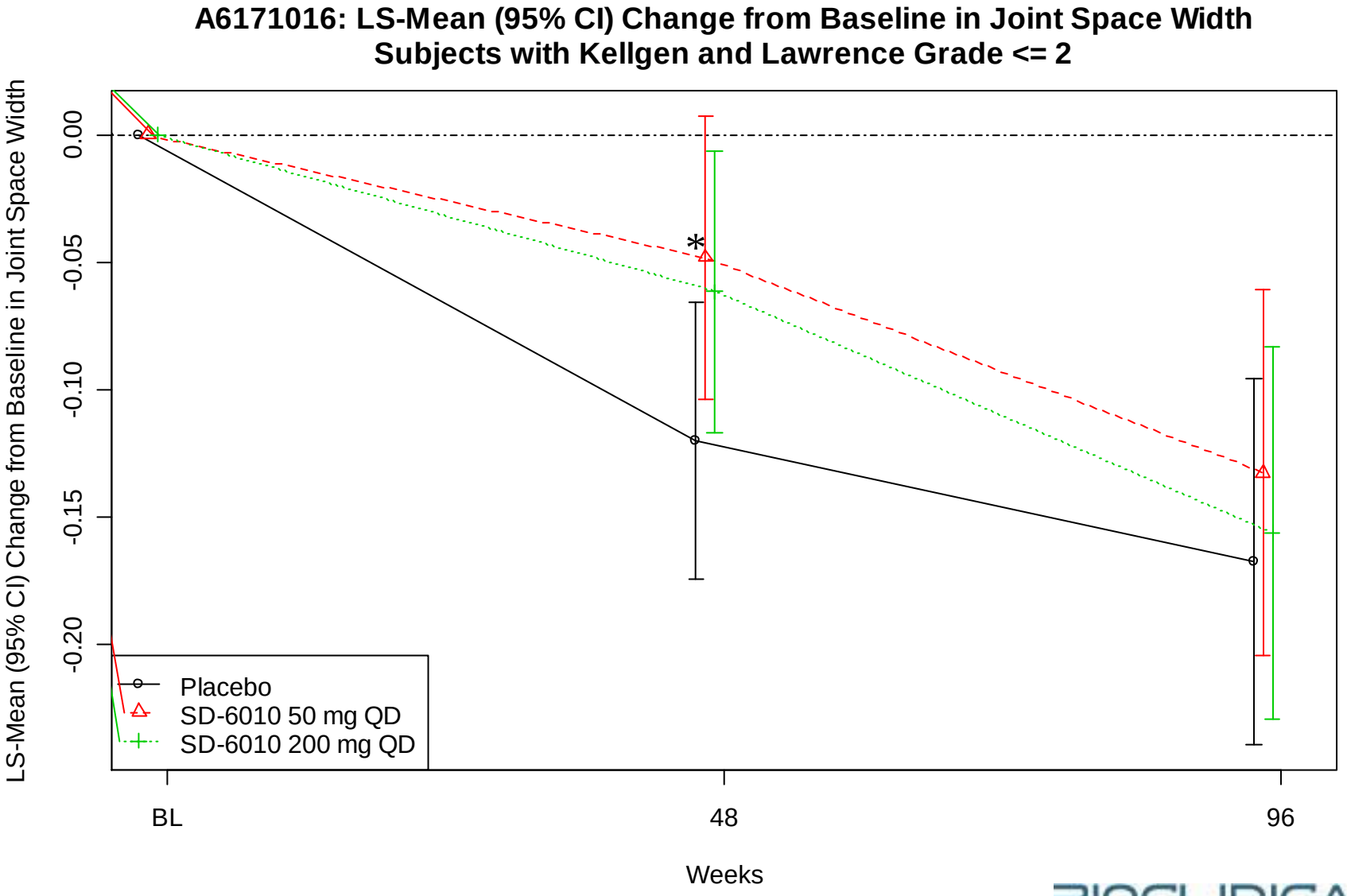
cindunistat Results: OARSI 2012



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Failure – Why?

- *Calcitonin failed on JSN Endpoint*
- *Failed Futility Analysis (placebo did not demonstrate significant change)*
- *2 Possible reasons:*
  - *Incorrect subject enrollment (poor KL scoring)*
  - *Poor QC of images so precision was decreased*
  - *Combination of both*

Conclusion: Where to next?

- *Diagnostic Sensitivity*
- *Precision/Accuracy*
- *Reliability*
- *Relevance*
- *Cost effective*
- *Acceptance by regulatory agencies - DRIVER*
- *Acceptable to Subject*
- *Safety to subject and operator*

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Conclusion

- ***Are we using the best surrogate?***
- ***Are we evaluating OA correctly?***
  - ***What is the pathophysiology?***
  - ***Should we sub categorize?***
- ***New Guidance Documents***
  - ***Validation of Biomarkers***
  - ***Standards for Clinical Trial Imaging End Points***
- ***Evaluate new BioMarkers Carefully***
  - ***Maximize the metrics!***