

Is the Modified Rodnan Skin Score an Outcome or a Surrogate in Trials of Therapies for Systemic Sclerosis?

The Case for Outcome

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Clinical Assessment of Skin Thickening- Modified Rodnan Skin Score

0	Uninvolved
1	Mild thickening
2	Moderate thickening
3	Severe thickening

Face	Upper arm	Upper arm	Anterior chest	Forearm	Forearm	Hand	Hand	Fingers	Fingers	Thigh	Thigh	Leg	Leg	Foot	Foot

Why do we do skin scores?

- Primary criterion for classification as diffuse vs limited
- Is your patient the same, better or worse?
- Symptomatic and functionally relevant to the patient

Fibrosis or Atrophy??



The OMERACT Filter for Outcome Measure Validation

- **Face Validity** – does it make sense?
- **Content Validity** – is it comprehensive?
- **Construct validity** – agree with other measures or with a “gold standard”? – ability to discriminate subsets?
- **Accuracy** - (criterion validity)
- **Reproducibility**
- **Sensitivity to change**
- **Feasibility**

Attributes of MRSS as Outcome Measure

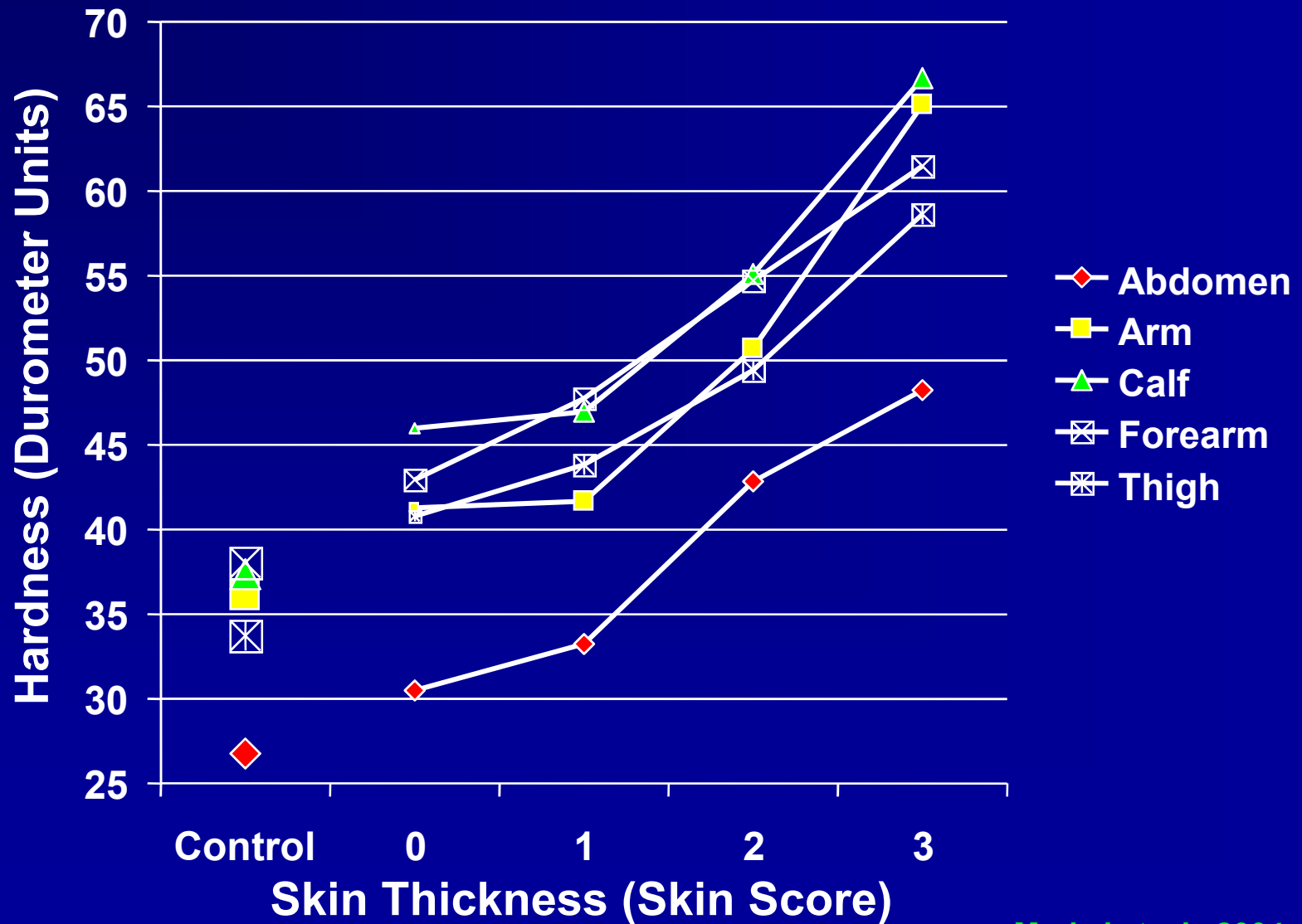
- **Accuracy: Interobserver variability 5 units**
- **Reproducibility: Intraobserver variability 3 units**
- **Accessibility: Clinical examination technique**
- **Sensitivity to Change: Characteristic**

Construct Validity of mRSS

- Strong correlation with core skin biopsy weights
- Local skin score $r=0.536$
- Total skin score $r=0.553$

141 subjects

Figure 1: Skin Thickness vs Skin Hardness



Clinical Meaningfulness of Change in MRSS

- Increase predicts worsening of SSc
- Stability predicts reduced new internal involvement
- Improvement predicts improved 5 and 10 year survival
- High scores (>20) predict renal crisis (OR 6.64)
- High scores (>20) predict mortality (OR 3.39)
- Improved TSS correlates with HAQ-DI, ROM, hemoglobin

CORE QUESTION – IS MRSS AN OUTCOME, A SURROGATE, OR BOTH?

Experts' Clinical Biases

- mRSS < 10 - total remission
- mRSS 11-35 - 50% improvement
- mRSS 35-51 - 35% improvement

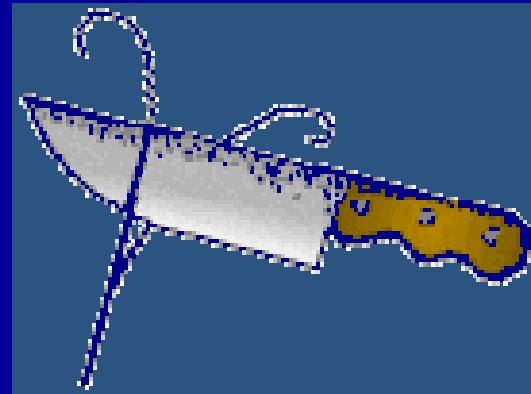
- Expert ratings of "clinical meaningfulness"

Heterogeneity of Disease

- Clinical syndrome is diverse
- Disease processes are diverse

- Is this a family of related disorders or is this a single disease in which genotype influences clinical phenotype?

Lumping versus Splitting



Predominant Features Associated with Scleroderma-Specific Autoantibodies

	ACA	Th/To	U1-RNP	PmScI	U3-RNP	Topo	Pol 3
SSc Subset	L	L	L	L	D	D	D
Lung	PH	ILD & PH	PH		ILD & PH	ILD	
Renal	-	-	-	-	+	+	+

Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum 35:35-42, 2005.

Goal – Precision

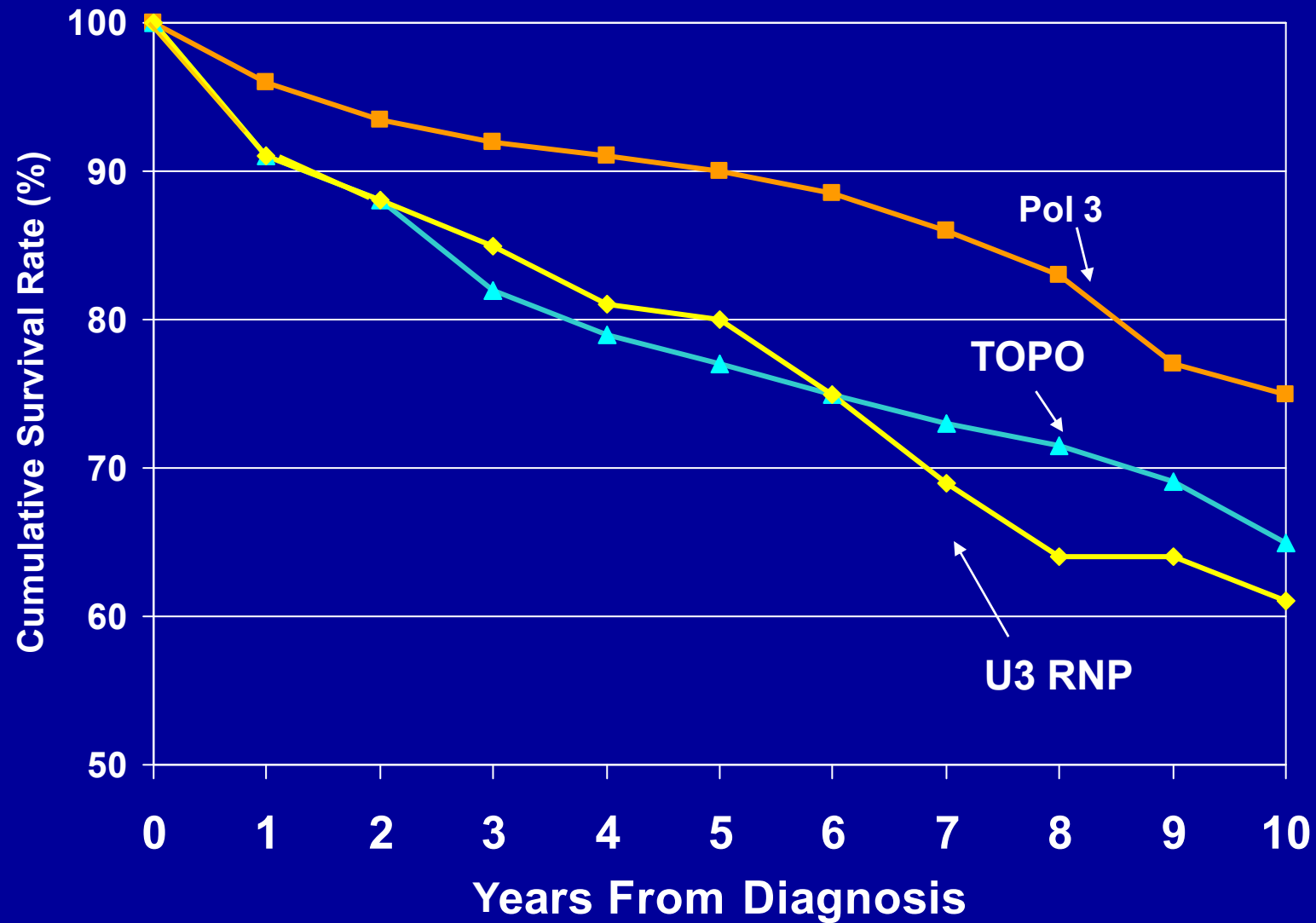
DRB*1104 and Anti-topoisomerase 1

Odds Ratio 7.0

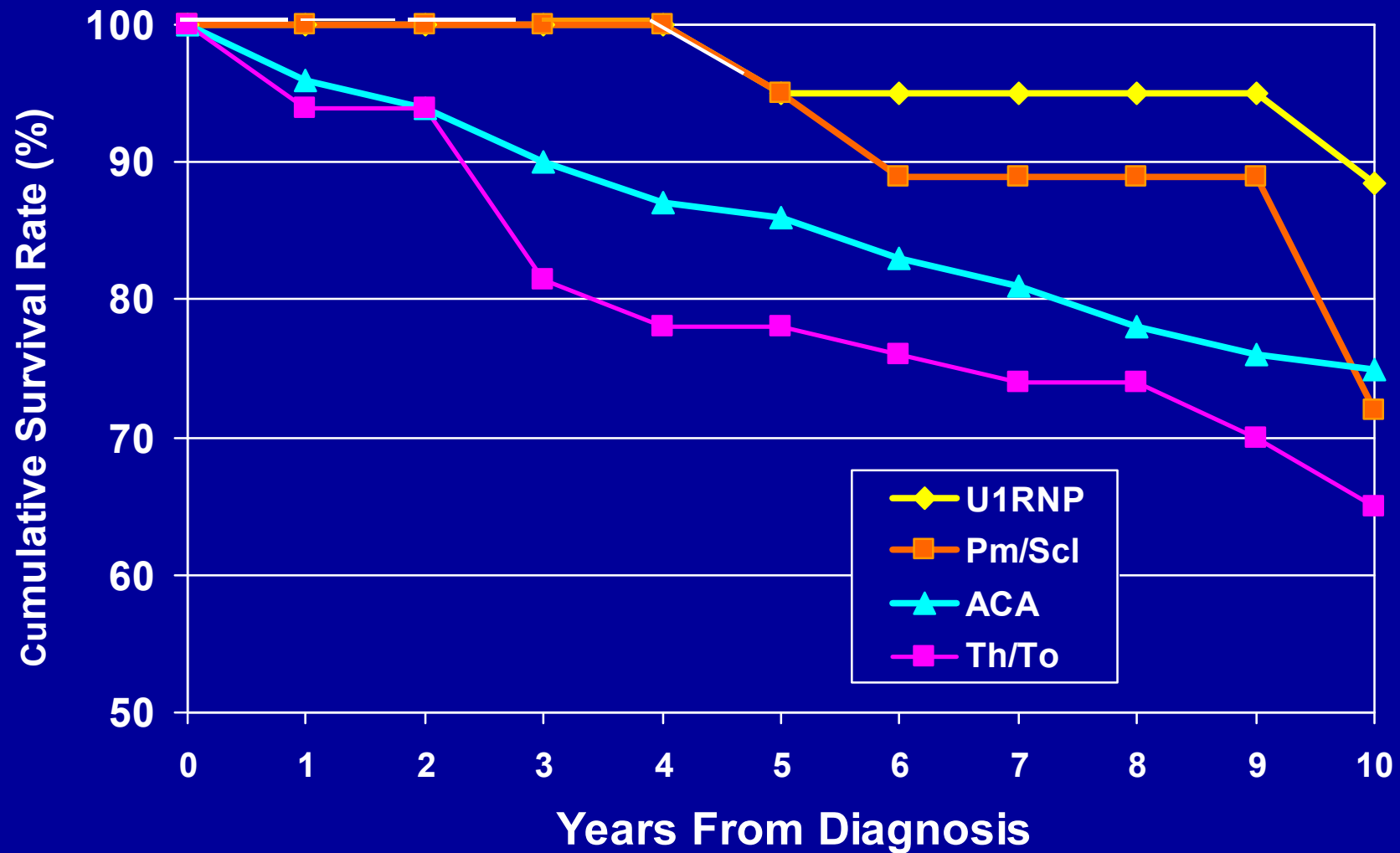
Skin Scores and Serologies

	<u>Initial</u>	<u>Peak</u>	<u>% Severe</u>
ACA	5	6	0
Th/To	4	4	0
U1 RNP	6	6	5
U3 RNP	15	16	26
Topo	18	19	32
Pol III	25	28	51

Survival in Diffuse Scleroderma Subsets



Survival in Limited Scleroderma Subsets



Severe Lung and Serologies

	<u>P Fib</u>	<u>Lowest FVC</u>	<u>PAH</u>
ACA	6%	87	19%
Th/To	16%	70	32%
U1 RNP	22%	75	14%
U3 RNP	24%	68	24%
Topo	23%	67	2%
Pol III	7%	81	6%

Renal Crisis and Serologies

	<u>ALL</u>	<u>Diffuse</u>
ACA	1%	0
Th/To	4%	0
U1 RNP	4%	10%
U3 RNP	7%	10%
Topo	10%	15%
Pol III	28%	33%

Skin

- Modified Rodnan Skin Score
- Visual analog scale (VAS) or /Likert of **patient** global assessment for skin activity (How active is your skin involvement due to scleroderma?)
- VAS or /Likert of **physician** global assessment for skin activity
- Durometer

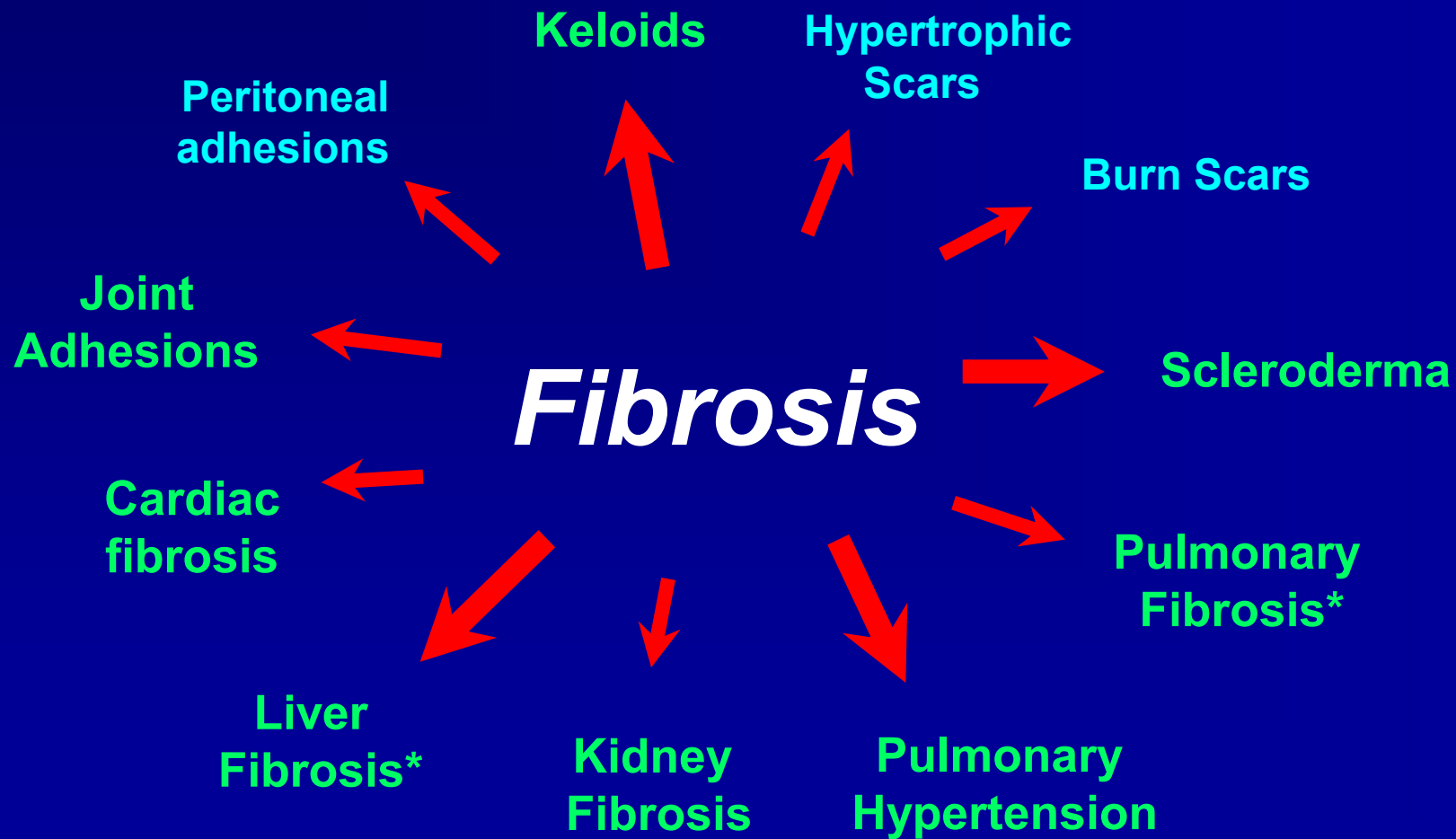
Standards of Approvability

- Are “Signs & Symptoms” Sufficient?
 - Total Skin Score
 - Function
 - Quality of Life
- Lack of Negative Visceral Trends

Scleroderma as Initial Indication

- **Unmet Medical Need**
- **Supportive Scientific Base**
- **Platform Disease**

Scleroderma as a Platform Disease: Potential Indications



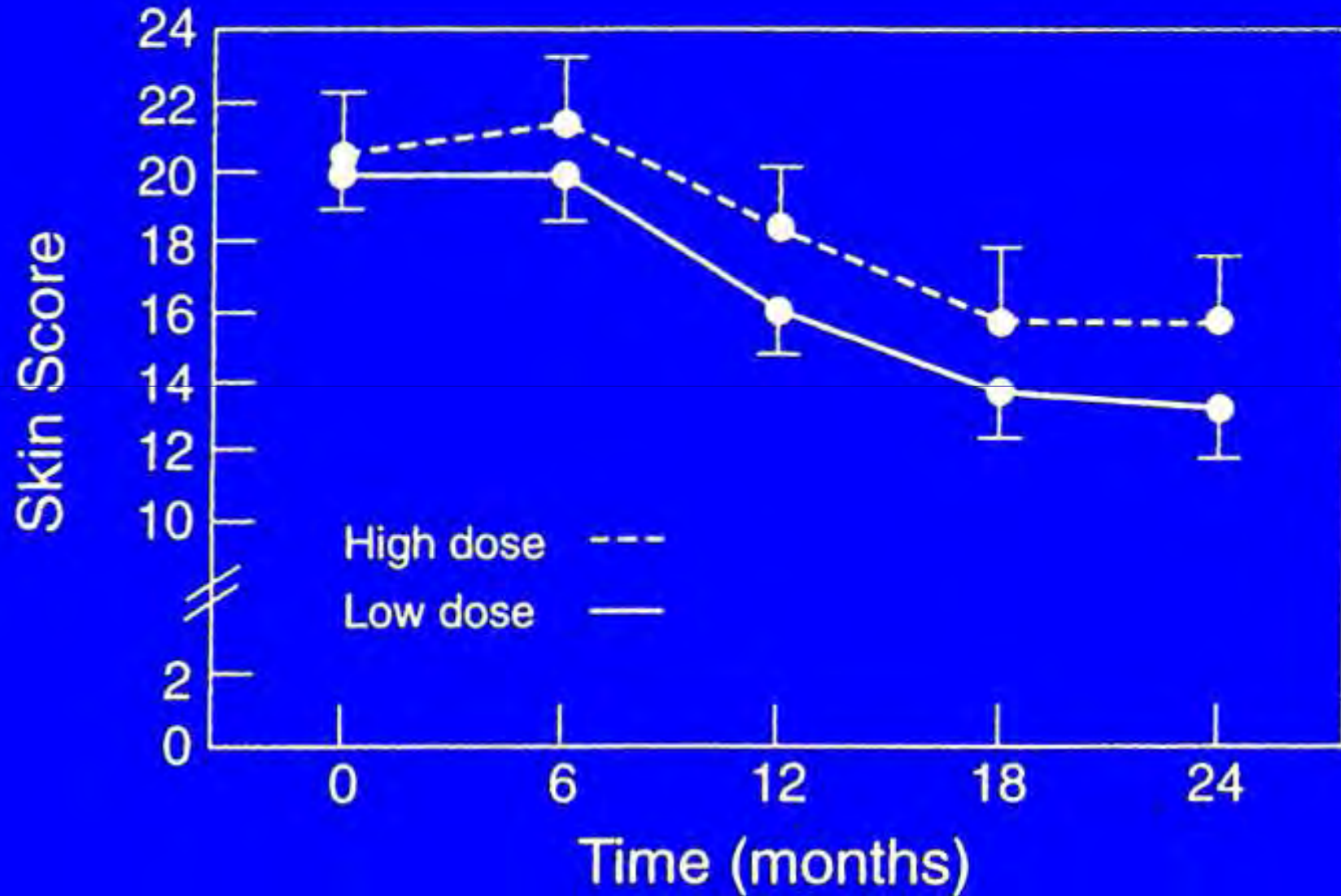
The Current Trial Template

- **Diffuse Scleroderma**
- **Defined Duration**
- **Defined Severity**
- **Excluded Drugs and Complications**
- **Total Skin Score**
- **Modified HAQ**
- **SF-36**
- **Patient and Physician Global**
- **Occurrence of New Visceral Disease**
- **Pulmonary Function, Dyspnea Index, Six Minute Walk**
- **?? Survival**

Candidate Approaches to SSc

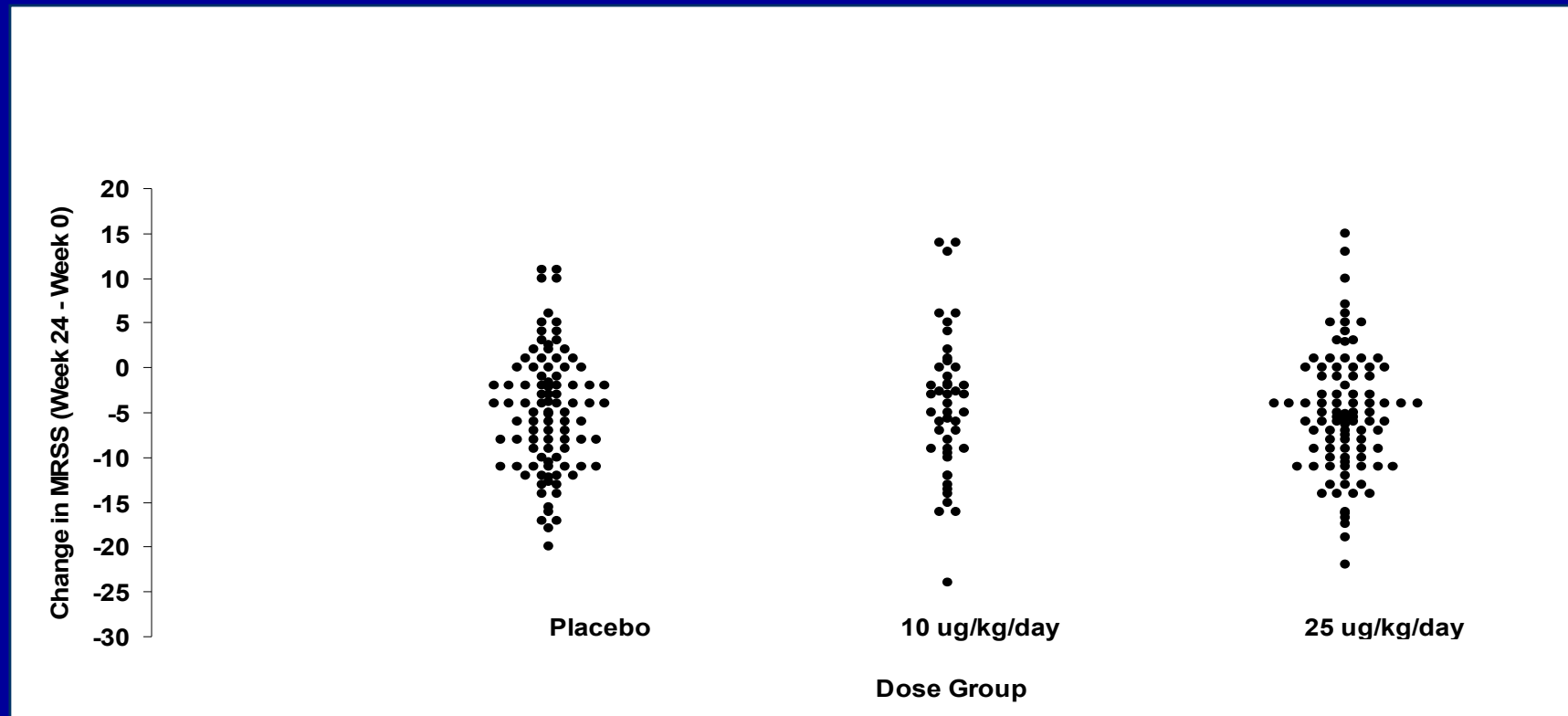
- **MRSS/HAQ/SF-36 (“Skin and Trends”)**
- **Organ-Specific**
- **Composite Response**
- **Survival**
- **Event Free Survival**

U.S. D-Penicillamine Trial



U.S. PHASE III STUDY OF RELAXIN

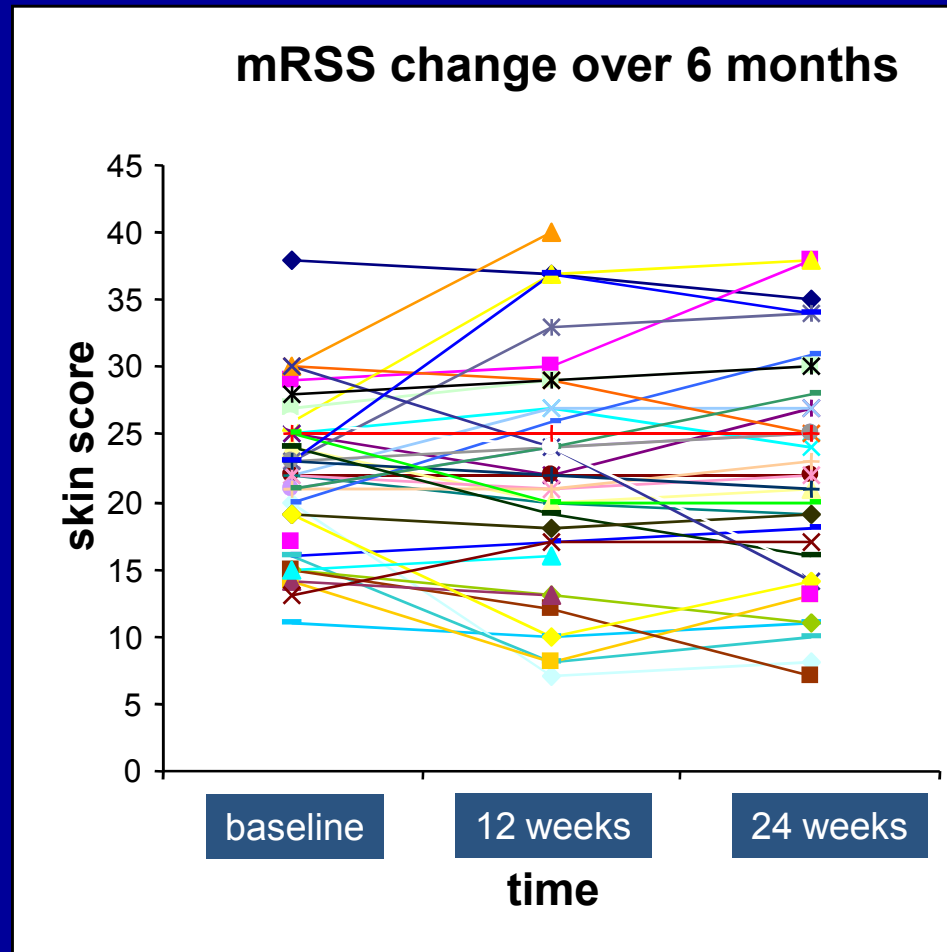
Dot Histogram by Dose Group for Change From Week 0 by Modified Rodnan Skin Score



Prevention versus Reversal

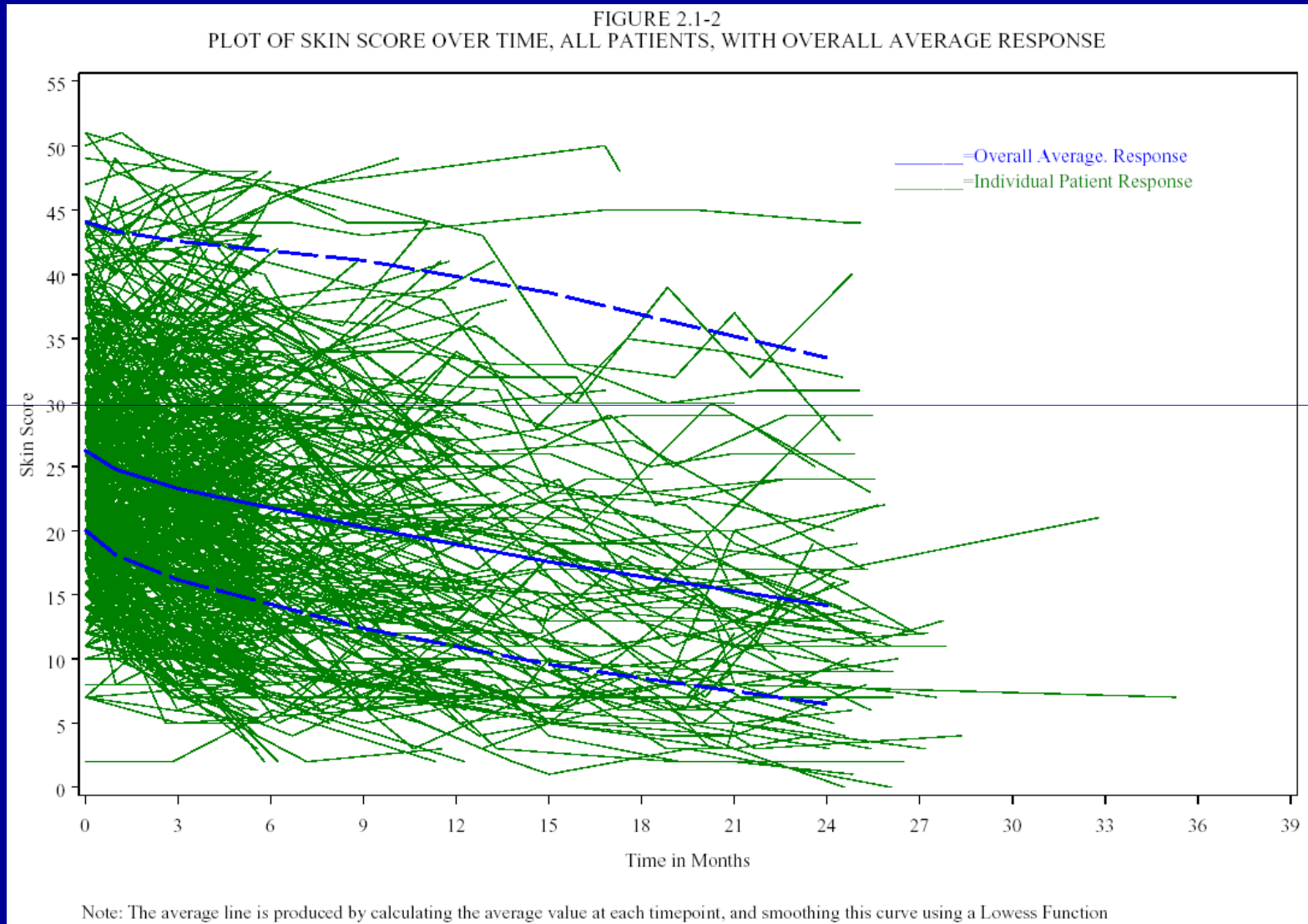


Change in modified Rodnan skin score over 6 months in the CAT192 anti-TGFβ-1 MAb trial for early dcSSc



Subjects with dcSSc (n=45) were enrolled and randomly allocated to receive placebo or CAT192 at 0, 6, 12 and 18 weeks.
Median (range) disease duration at baseline 6.4 (0.3-22.5) months

Plot of Individual Patient mRSS over Time



Metrics of TSS as Outcome Variable

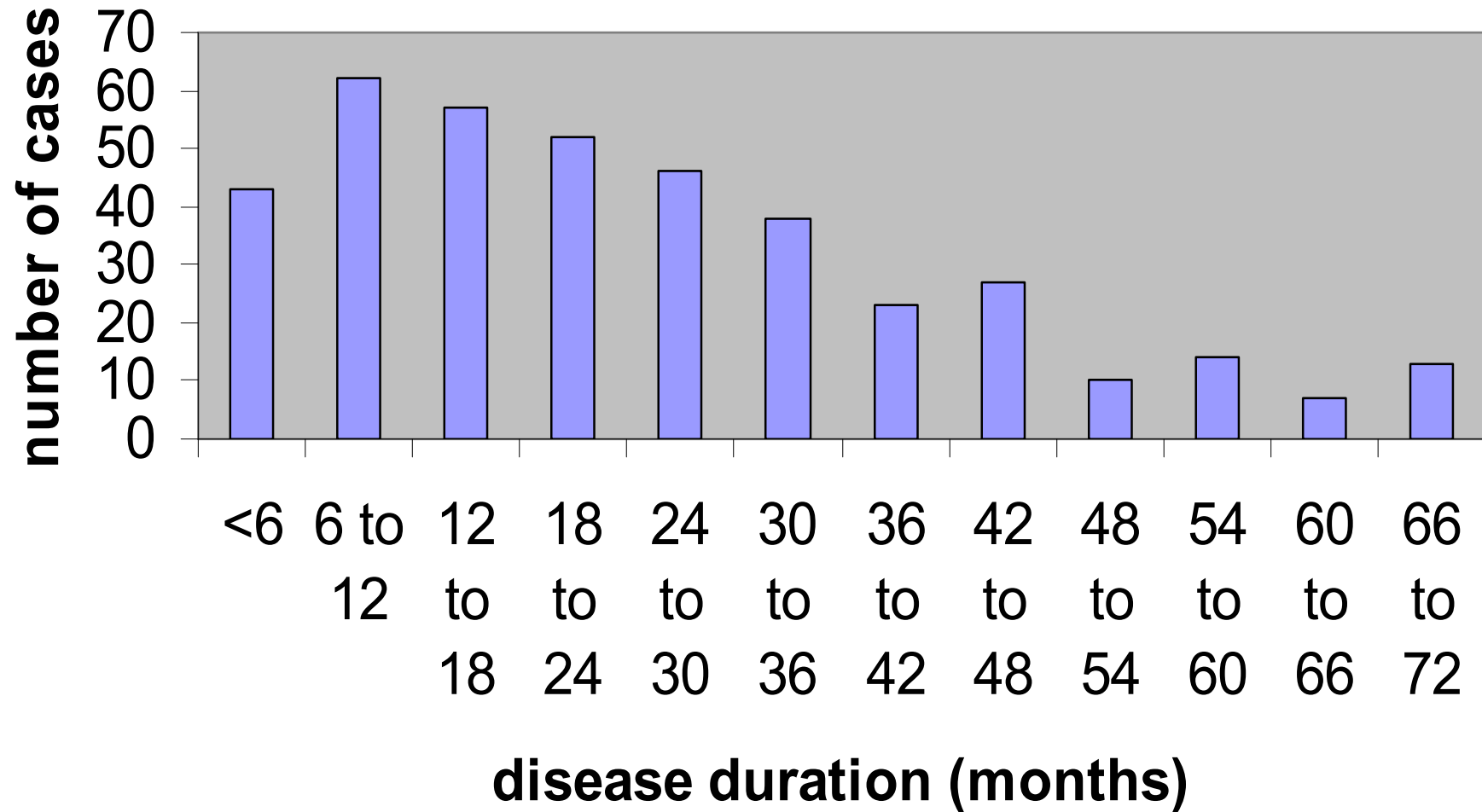
Year 1.....	Worsens
Year 2.....	Unchanged
Year 3-4.....	Improves*

Prevention.....	Year 1
Reversal.....	Year 2 – 4

Effect required > 35%

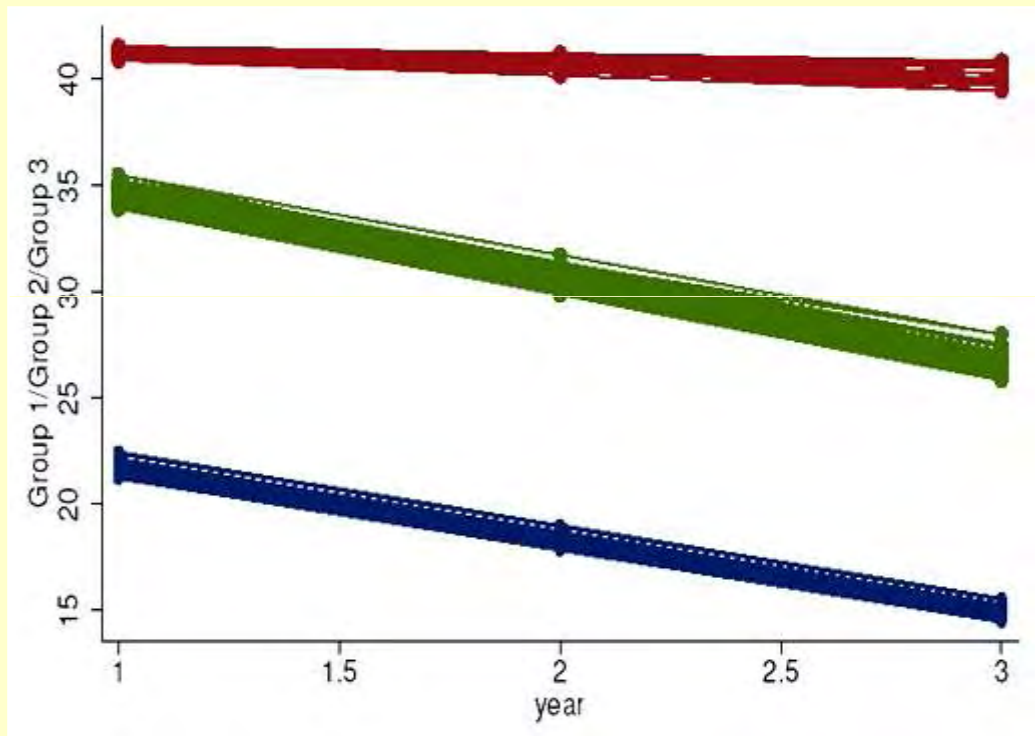
*Improvement 5 units per 6 months

Duration of disease in dcSSc at peak skin score



Latent Linear Trajectory Models

3 subgroups



n=24
Gp 3

“bad”

n=40
Gp2

“intermediate”

n= 67
Gp1

“good”

Unclassified, n=61 (less than 90% probability of fitting into any subgroup)

Why does skin improve?

- ?Because it can?
- Does the stimulus abate?
- Do host factors influence durability of response?
- Is it improvement or atrophy?
- Is skin a “window” on other tissues?

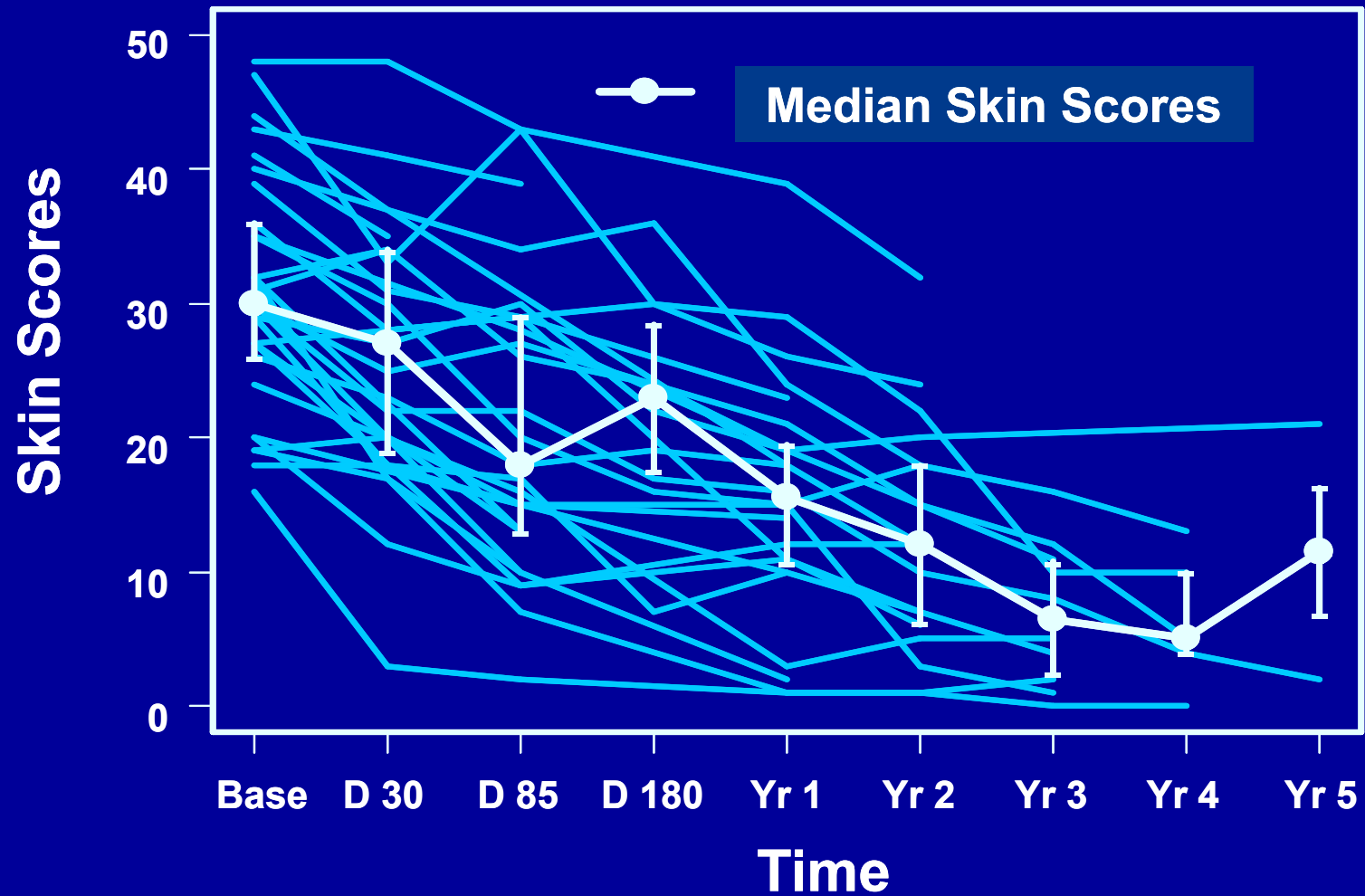
Can We Predict Worsening?

- Recent increase TSS
- Multiple tendon friction rubs
- Anti-topoisomerase I, U1 RNP, U3 RNP
- Elevated soluble IL-2 receptor
- Histopathology
- CPK
- Hemoglobin
- ESR

Specificity versus Aggression



U.S. Pilot Trial of HDIT with Reconstitution



Is Skin an Outcome or a Surrogate?

Fast Track Guidance Standards:

A preventative product would be considered to treat a serious condition if (i) it is being evaluated for its ability to prevent a serious manifestation or (ii) it is being studied for its ability to prevent the condition and it is scientifically reasonable to assume that prevention of the condition would prevent its serious consequences.