The MOdified NARanjo Causality Scale for ICSRs (MONARCSi): A Decision Support Tool for Safety Scientists
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Online Resource 2 MONARCSI and Naranjo: A Comparison

Features included in MONARCSi compared to Naranjo
Online Resource 3 provides a detailed review of each feature included in the MONARCSi tool in comparison to the original Naranjo score. The MONARCSi scale is designed to be used in the clinical trial setting. Consequently, three features from Naranjo that were not considered likely relevant or known in the clinical trial setting by Roche safety professionals, have been excluded empirically from the MONARCSi scale (Previous Reaction, Toxic Blood Levels, and Placebo Reaction). Two additional features not included in Naranjo are considered particularly relevant in the clinical trial setting by Roche safety professionals and have been added to MONARCSi (Mechanism of Action and Significant Safety Event). Mechanism of Action is often known or hypothesized in the clinical trial setting of designed drugs or molecules and so it is important to potentially link possible adverse effects to the presumed biologic activity. In addition, the Significant Safety Event feature captures a subset of Significant Safety Events from the Food and Drug Administration's and European Medicines Agency's list of Designated Medical Events. Our specific source for these are taken from Klepper and Cobert's book on Drug Safety Data.[1] The list of Significant Safety Events for MONARCSi is included in Online Resource 7.

Weights in MONARCSi compared to weights in Naranjo
It would be interesting to directly compare the weights in MONARCSi compared to the original Naranjo score weights. However, it is not possible based on the available published literature In the original paper describing the Naranjo score, [18] the authors state that six observers independently assigned a weighted score (i.e., integers ranging from -1 to +2) to the individual components of the Naranjo scale and these weighted scores were then used to establish a causal association. Unfortunately, Naranjo did not describe further information about the method of aggregation and meaning of the individual weights in the original paper. Review of the medical literature reveals no further information about weighting methods or details of the original cases. This lack of information has posed difficulties for researchers wanting to further evaluate Naranjo for use in critical care, overdose and other clinical settings.[2] The MONARCSi score weights were developed by asking safety professionals that regularly perform company causality assessments of drug-event pairs to evaluate how important the presence or absence of the included Bradford-Hill/Naranjo concepts were for their decision making. The results show that MONARCSi scores averaged across the 65 independent surveyed safety professionals ranged from absolute values of 1.23 to 3.66 on a 0 to 4 scale where 0 = no weighting importance and 4 = very high weighting importance. An *ad hoc* statistical evaluation showed no obvious differences between the average feature weightings of safety professionals based on therapeutic work area and geography. It is interesting to note that while some features were weighted very highly when present (e.g., Significant Safety Event at 3.58), others such as Temporality were weighted lower at 2.42 for presence and 2.00 for absence of Temporality. Similar to the parent Naranjo scale, if the temporality weighting is low other present features may be enough to outweigh the lack of temporality and support a causal judgment when the event occurred prior to use of the drug. There were only 11 out of 978 (1.1%) drug event pairs where there was not a temporal relationship in our dataset so the impact of this lower weighting would have been small. However, for use in a production environment we would propose 'hyper-weighting' the absence of this feature beyond our 5-point ordinal scale to an absolute value of 20. This hyperweight biases the causality assessment towards one that most of the pharmacovigilance community would accept when there is no temporal relationship (i.e., Not Related). Online Resources 8 and 9 provide additional examples of the Naranjo and MONARCSi scores including assessments of causality.

Additional Validation Testing: Directly Comparing Raw Scores from MONARCSi and Naranjo
A direct comparison of raw scores between MONARCSi and Naranjo for the same cases is not possible because the features differ between the two instruments, as described above. Thus, we compared the resulting raw scores between MONARCSi and Naranjo by using a restricted set of the seven Naranjo features that overlapped with MONARCSi. The results of this exercise using the MONARCSi final test dataset of 187 ICSRs showed high correlation (0.88) with an adjusted r-squared of 0.77. Additionally, binary classification of this same dataset was

performed using the restricted Naranjo score by classifying ICSRs with Naranjo scores greater than 4 ("Probable") as "Related" and all scores below this as "Not Related". The resulting confusion matrix comparison to MONARCSi shows high agreement (gKappa = 0.82). Online Resources 4, 5 and 6 provide further details on this concurrent validation testing. In summary, these comparisons show high agreement and correlation between MONARCSi and the Naranjo scale and support the validity of the MONARCSi instrument as a decision support tool for assessing causality.

1. Klepper MJ, Cobert B. Drug safety data: How to analyze, summarize, and interpret to determine risk. Sudbury, MA; Jones & Bartlett Learning; 2011.

2. Seger D, Barker K, McNaughton C. Misuse of the Naranjo Adverse Drug Reaction probability scale in toxicology. Clin Tox. 2013; 51(6):461-466.

Online Resource 3 Comparison of the MONARCSi and Naranjo score features.

Feature Description	Present in MONARCSi?	MONARCSi Feature Question	Present in Naranjo?	Corresponding Naranjo Feature Question	Comments
Significant Safety Event	Yes	Is this adverse event consistent with a Significant Safety Event (SSE) associated with drug/molecule use (e.g., SJS, DILI, etc.)?	No	Not applicable	The SSE concept is not in the Naranjo scale. Events are taken from Klepper et al 2011[1]—see Online Resource 10.
Previous Association	Yes	Are there previous reports on this adverse reaction with this drug/class supporting a causal relationship?	Yes	Are there previous conclusive reports on this reaction?	Similar concept in both instruments, but with different wording.
Temporality	Yes	Is the AE onset temporally associated with drug/molecule use?	Yes	Did the adverse event appear after the drug was given?	Similar concept in both instruments, but with different wording.
Mechanism of Action (MOA)	Yes	Is the AE consistent with the known drug/molecule mechanism of action?	No	Not applicable	Naranjo does not include consistency with the drug/molecule MOA (biologic plausibility). This feature is considered relevant in the clinical trial setting when the mechanism of action may be known and linking with biologic activity may be important.
De-Challenge	Yes	Did the AE resolve/improve with drug/molecule De-Challenge?	Yes	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Similar concept in both instruments, but with different wording
Re-Challenge	Yes	Did AE recur with drug/molecule Re-Challenge?	Yes	Did the adverse reaction reappear upon re-administering the drug?	Similar concept in both instruments, but with different wording
Dose Response	Yes	Was the AE affected by dosing changes (i.e., increase/decrease)?	Yes	Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	Similar concept in both instruments, but with different wording

Feature Description	Present in MONARCSi?	MONARCSi Feature Question	Present in Naranjo?	Corresponding Naranjo Feature Question	Comments
Experimental Evidence	Yes	Are other data (i.e., labs, imaging, preclinical, or experimental results) present that support a causal relationship?	Yes	Was the adverse event confirmed by any other objective evidence?	Similar concept in both instruments (called “Objective Evidence” in Naranjo), but with different wording
Confounding	Yes	Are alternative explanatory causes/confounding factors for the AE present?	Yes	Were there other possible causes for the reaction?	Similar concept in both instruments, but with different wording
Previous Reaction	No	Not applicable	Yes	Did the patient have a similar reaction to the drug or a related agent in the past?	Not included in MONARCSi which is designed for use in clinical trials where past reactions to similar experimental drugs are usually not known
Toxic Blood Levels	No	Not applicable	Yes	Was the drug detected in the blood or other fluids in toxic concentrations?	Not included in MONARCSi which is designed for use in clinical trials where established therapeutic and toxic drug levels typically are not fully established yet
Placebo Reaction	No	Not applicable	Yes	Did the adverse reaction reappear upon administration of placebo?	Not included in MONARCSi which is designed for use in clinical trials which usually do not treat with placebo after active treatment

Online Resource 4 Results from 'direct comparison' of MONARCSi (Reference system) and Naranjo* (Test system) for 187 test drug-event pairs.

Naranjo (Reference system) vs MONARCSi (Test system) Classification Counts				
Binary Classification Task (Yes/no)?		**MONARCSi**		
		Yes	**No**	**Totals**
Naranjo	**Yes**	24	5	29
	No	18	140	158
	Totals	42	145	187

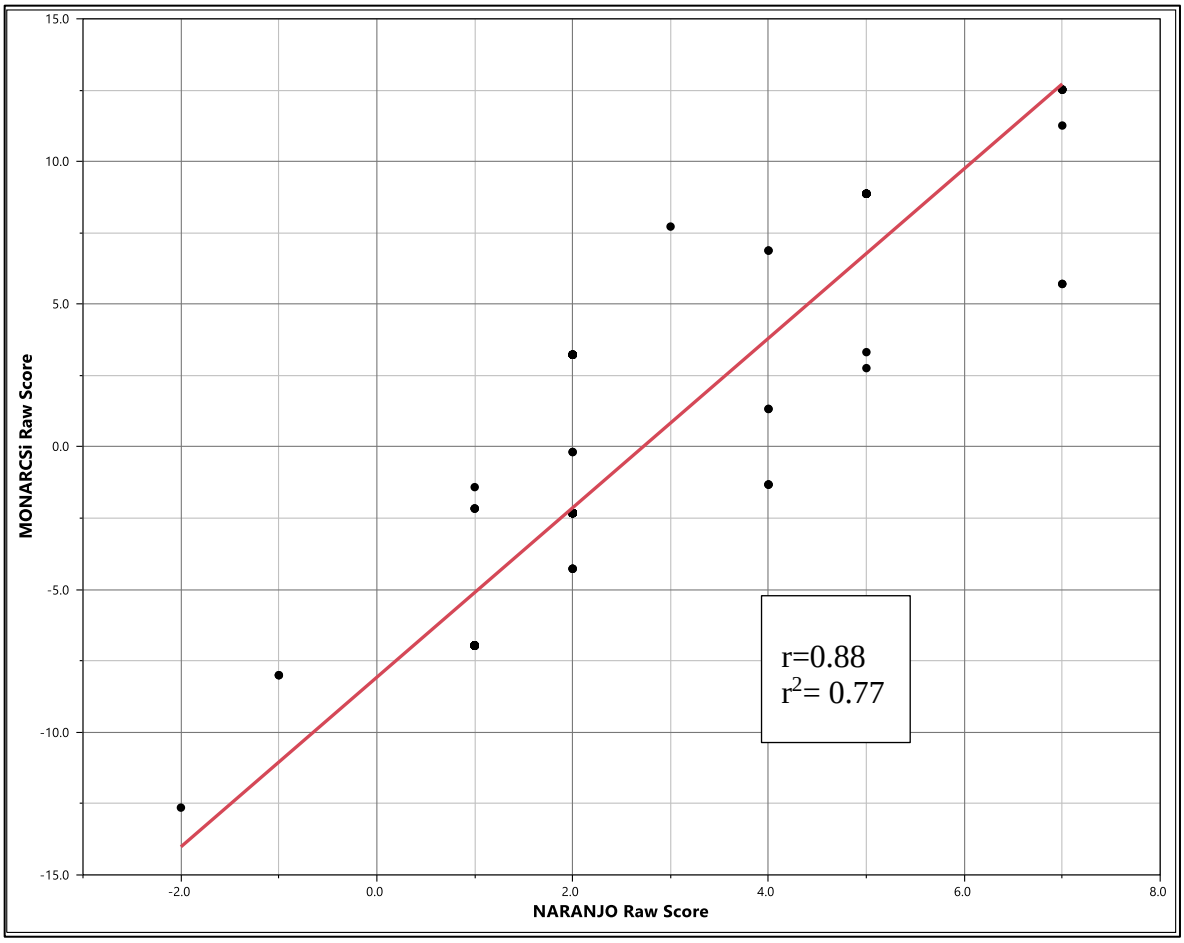
*Used abbreviated Naranjo based on seven overlapping features of MONARCSi and Naranjo

Online Resource 5 Results of validation testing of MONARCSi and Naranjo* (for 187 test drug-event pairs)**.**

Performance Metric	**Value**
Sensitivity % Positive Agreement	82.8%
Specificity % Negative Agreement	88.6%
Positive Predictive Value (Precision) Proportion of true "related" out of all classified "related"	57.1%
Negative Predictive Value Proportion of true "unrelated" out of all classified "unrelated"	96.6%
gKappa Score Inter-rater agreement	82.2%

*Used abbreviated Naranjo based on seven overlapping features of MONARCSi and Naranjo

Online Resource 6 Raw score comparison of MONARCS vs. Naranjo (seven overlapping features)



Online Resource 7 Significant Safety Events (SSE): Subset of designated medical events (DME) with '*a priori'* elevated index of suspicion for drug-event pair relatedness.[1]

MedDRA Preferred Term	MedDRA System Organ Class
Agranulocytosis	Blood and Lymphatic Disorders
Aplastic Anemia	Blood and Lymphatic Disorders
Ventricular Fibrillation	Cardiac Disorders
Ventricular Tachycardia	Cardiac Disorders
Torsades de Pointes	Cardiac Disorders
Congenital Anomalies	Congenital, Familial, and Genetic Disorders
Pancreatitis	Gastrointestinal Disorders
Injection Site Reactions	General Disorders and Administration Site Conditions
Acute Liver Failure	Hepatobiliary Disorders
Liver Necrosis	Hepatobiliary Disorders
Anaphylaxis	Immune System Disorders
Rhabdomyolysis	Musculoskeletal and Connective Tissue Disorders
Neuroleptic Malignant Syndrome	Nervous System Disorders
Progressive Multi-focal Leukoencephalopathy (PML)	Nervous System Disorders
Seizure	Nervous System Disorders
Acute Renal Failure	Renal and Urinary Disorders
Acute Respiratory Failure	Respiratory Thoracic and Mediastinal Disorders
Pulmonary Fibrosis	Respiratory Thoracic and Mediastinal Disorders
Pulmonary Hypertension	Respiratory Thoracic and Mediastinal Disorders
Erythema Multiforme	Skin and Subcutaneous Tissue Disorders
Stevens-Johnson Syndrome	Skin and Subcutaneous Tissue Disorders
Epidermal Necrolysis	Skin and Subcutaneous Tissue Disorders
Fixed Drug Reaction	Skin and Subcutaneous Tissue Disorders
Malignant Hypertension	Vascular Disorders

Online Resource 8 An Example of The Naranjo Causality Score

Naranjo Causality Scale			Weights			ICSR Choices			Raw Score
Number	**Concept**	**Questions**	**Yes**	**No**	**UNK/ NA**	**Yes**	**No**	**UNK/ NA**	**Value**
1	Previous Association	Are there previous conclusive reports on this reaction?	1	0	0	1	0	0	1
2	Temporality	Did the adverse event appear after the suspected drug was administered?	2	-1	0	1	0	0	2
3	De-Challenge	Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	1	0	0	1
4	Re-Challenge	Did the adverse event reappear when the drug was re-administered?	2	-1	0	1	0	0	2
5	Confounding	Are there alternative causes that could on their own have caused the reaction?	-1	2	0	0	0	1	0
6	Placebo	Did the reaction reappear when a placebo was given?	-1	1	0	0	0	1	0
7	Drug Levels	Was the drug detected in blood or other fluids in concentrations known to be toxic?	1	0	0	1	0	0	1
8	Dose Response	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	0	0	1	0
9	Drug Class	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	1	0	0	1
10	Objective evidence for AE?	Was the adverse event confirmed by objective evidence?	1	0	0	1	0	0	1
Total Naranjo Score (Range = -4 to 13)									**9**
Causal Probability Threshold									**≥5 probable ≥9 definite**
Causality Classification									**Probable**

Online Resource 9 An Example of the MONARCSi Causality Score

MONARCSi Causality Scale			Weights			ICSR Choices			Raw Score
Number	**Concept**	**Questions**	**Yes**	**No**	**UNK/NA**	**Yes**	**No**	**UNK/NA**	**Value**
1	Significant Safety Event (SSE)	Is this adverse event consistent with an SSE associated with drug/molecule use?	**3.58**	**-1.23**	**0.00**	0	1	0	**-1.23**
2	Previous Association (PVA)	Are there previous reports on this adverse reaction with this drug/class that support a causal relationship?	**3.42**	**-2.14**	**0.00**	0	1	0	**-2.14**
3	Temporality (TMP)	Is the adverse event onset temporarily associated with drug/molecule use?	**2.42**	**-20.00***	**0.00**	1	0	0	**2.42**
4	Mechanism of Action (MOA)	Is the adverse event consistent with drug/molecule mechanism of action?	**3.66**	**-2.95**	**0.00**	0	1	0	**-2.95**
5	De-Challenge (DEC)	Did the adverse event resolve or improve when the drug/molecule was discontinued, or a specific antagonist was administered?	**2.77**	**-2.92**	**0.00**	1	0	0	**2.77**
6	Re-Challenge (REC)	Did the adverse event recur when the drug/molecule was re-administered?	**2.86**	**-1.80**	**0.00**	1	0	0	**7.00**
7	Dose Response (DRS)	Was the adverse event affected by dosing changes, either increase or decrease?	**2.63**	**-1.89**	**0.00**	0	0	1	**0.00**
8	Experimental Data (EXP)	Are other data present that support a causal relationship?	**2.89**	**-1.72**	**0.00**	0	1	0	**-1.72**
9	Confounding Factors (CNF)	Are there alternative explanatory causes or confounding factors for the adverse event present?	**-2.69**	**2.95**	**0.00**	1	0	0	**-2.69**
Total MONARCSi Score (Range = -20 to 27)									**1.46**
Causality Probability Threshold									**>0.45**
Causal Classification									**Related**

*Note that this feature has been ‘Hyper-Weighted’ for the reasons discussed in Online Resource 2