MDDT Summary of Evidence and Basis of Qualification Decision for OsiriX CDE Software Module

Background

MDDT Name: OsiriX CDE Software Module

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TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

The OsiriX CDE consists of a software module that assists expert raters, e.g., neuroradiologists, by providing a standardized way to demarcate and classify brain contusions using Common Data Element (CDE) criteria and to label abnormalities on MR images. Brain contusions measured by expert readers using the OsiriX CDE Software Module may be used as an enrichment tool for enrollment in clinical trials of therapeutic medical devices intended to improve outcomes of mild traumatic brain injury (TBI) patients.

In this summary, the term enrichment means the prospective use of any patient characteristic to select a study population in which detection of a medical device effect (if one is in fact present) is more likely than it would be in an unselected population.

MR acquisition protocols intended for evaluation include:

- T2*-weighted gradient echo or susceptibility-weighted images (T2*)
- T2-weighted spin-echo (T2)
- T2-weighted Fluid Attenuation Inversion Recovery (FLAIR)
- 3D T1-weighted gradient echo (3D T1)

From the NINDS Common Data Elements[1]:

> Contusion is defined as a focal area of brain parenchymal disruption due to acute mechanical deformation. Contusions typically occur in the cortex and may extend into subcortical region. Contusions may show grossly visible hemorrhage or minimal/absent hemorrhage. Acute contusions typically have a mottled, inhomogeneous appearance due to stippling of blood along the brain surface. As such, their size is difficult to measure. In addition, CT streak artifact limits visualization of the cortical surface, so contusions are best seen with MRI, particularly on the Fluid Attenuation Inversion Recovery (FLAIR) sequence. For purposes of categorization, contusions are differentiated from "intracerebral hematomas" by containing a *mixture* of hemorrhagic and non-hemorrhagic tissue, or by having no grossly visible hemorrhage ("bland contusion"), while an "intracerebral hematoma" is predominantly a uniform collection of blood alone. The term "contusion" should not be used for hemorrhagic lesions which fit better in other categories, such as small hemorrhages associated with the pattern of diffuse axonal injury, lesions which in context are more likely to represent infarction or other primary vascular lesion, or isolated subarachnoid hemorrhage (SAH). Contusions can, however, be associated with other lesions which commonly co-occur, such as brain laceration, adjacent SAH, and depressed skull fractures. Contusions which are questionable, such as those in an area of beam hardening on CT scan, should be noted as "indeterminate". Note: areas of delayed hypodensity or signal change around a traumatic lesion should not necessarily be classified as contusions. Contusions in which the hemorrhagic component enlarges over time should not be re-classified on subsequent images as "intraparenchymal hemorrhage".

While there are possible advantages for using the OsiriX CDE Software Module MDDT for enrichment of a clinical trial, it is important to understand the possible disadvantages and limitations as well. The user of this MDDT should refer to the sections *Summary of Evidence to Support Qualification* and *Assessment of Advantages/Disadvantages of Qualification* to evaluate the totality of the information provided to determine the appropriate use of the MDDT for their application.

QUALIFIED CONTEXT OF USE

Contusions, as assessed by an expert rater from MRI using OsiriX CDE Software Module MDDT, may be used for enrichment of clinical trials for therapeutic medical devices intended to improve outcomes at 3 months for patients aged between 18-65 years with acute non-penetrating head trauma and Glasgow Coma Scale (GCS) 13-15 who have undergone acute head CT (e.g., as part of standard clinical care) at a U.S. Level 1 trauma center.

SUMMARY OF EVIDENCE TO SUPPORT QUALIFICATION

To support the qualification of the MDDT, the requestor provided a two part clinical study as described in the section below. In addition to the clinical study, previous investigations and pilot studies[2, 3], level of risk associated with the use of the MDDT, and the possible advantages/disadvantages were used as evidence to support qualification for enrichment in clinical trials.

Biomarker-Outcome Association Study Overview

Extended Glasgow Outcome Scale (GOS-E) at three months was analyzed in relation to the presence vs absence of 1) ≥1 brain contusion and/or 2) ≥4 diffuse axonal injury (DAI). The presence of these radiologic findings was determined independently by three (3) board-certified neuroradiologists and annotated using OsiriX CDE software module. MR images were acquired on 3T systems from multiple vendors.

Study population and Inclusion Criteria

The study included 517 patients between the ages of 18-65 who presented to the emergency department (ED) at one of 11 U.S. Level 1 trauma centers. The patients had acute non-penetrating head trauma that prompted the physician to order a head CT scan within 24 hours of injury and a Glasgow Coma Scale (GCS) ED arrival scores of 13-15, and completion of both 2-week MRI exam and 3-month GOS-E score.

Protocol violation

One of the 11 original study sites was excluded from the MDDT study population due to concerns that GOS-E was not administered according to standard study protocols.

Study Objective

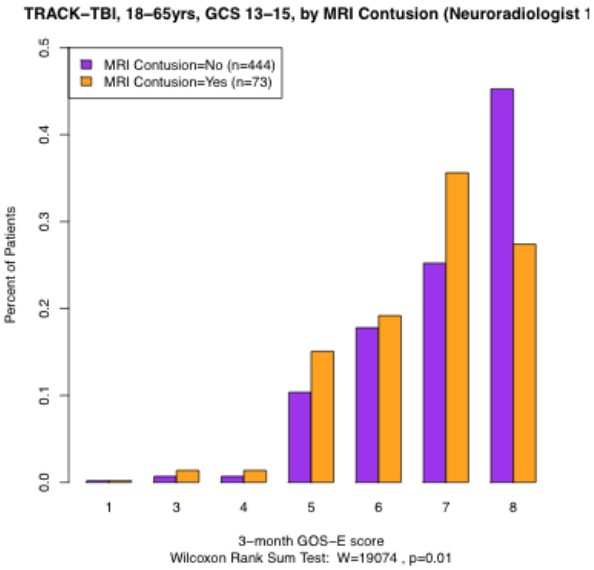
The objective of the study was to evaluate the association between contusions and DAI with 3-month GOS-E outcomes.

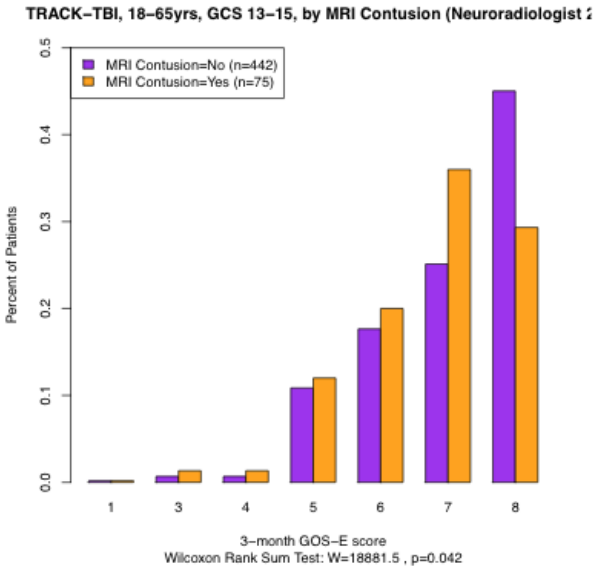
Results

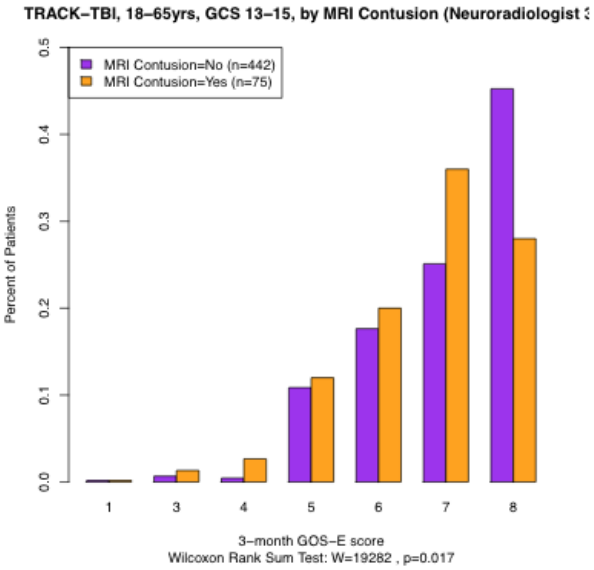
The study compared the 3-month GOS-E outcomes with the biomarker outcome using the Wilcoxon Rank Sum test for each neuroradiologist and biomarker (See Figures below). The Wilcoxon Rank Sum Test can be rescaled by dividing the number of patients with a contusion and by the number of patients without a contusion. This rescaling yields a number that is equivalent to AUC, the area under the ROC curve, (a probability) such that 0.5 indicates no relationship.

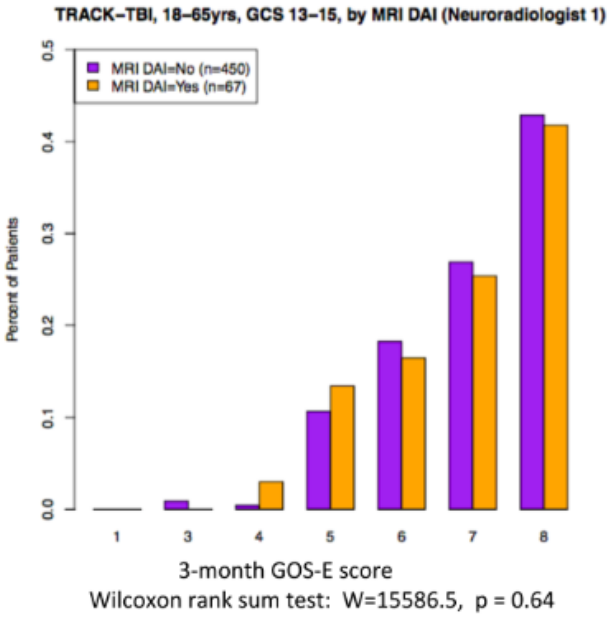
	MRI Contusion Biomarker			
	Positive	Negative	Wilcoxon	AUC (Rescaled Wilcoxon)
Reader 1	73	444	19074.0	0.588
Reader 2	75	442	18881.5	0.570
Reader 3	75	442	19282.0	0.582

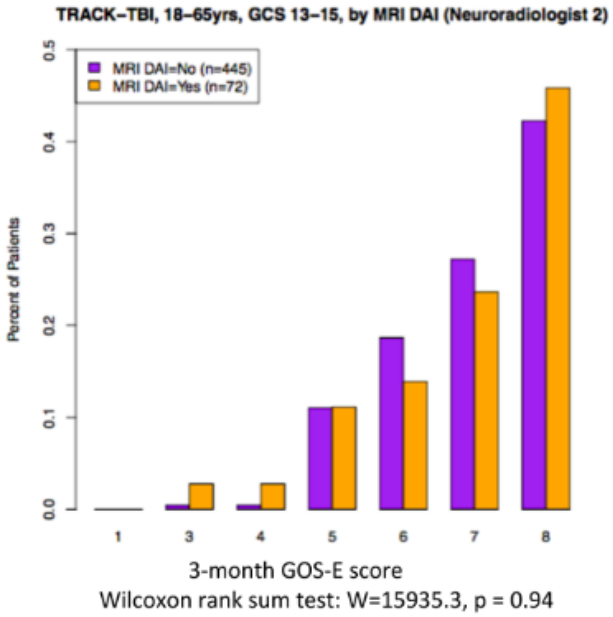
	MRI DAI Biomarker			
	Positive	Negative	Wilcoxon	AUC (Rescaled Wilcoxon)
Reader 1	67	450	15586.5	0.517
Reader 2	72	445	15935.3	0.497
Reader 3	50	467	11675.0	0.500

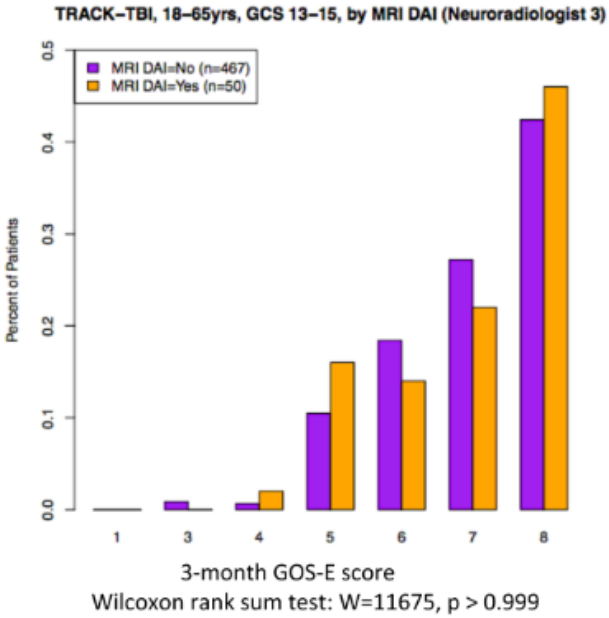

TRACK–TBI, 18–65yrs, GCS 13–15, by MRI Contusion (Neuroradiologist 1
MRI Contusion=No (n=444)
MRI Contusion=Yes (n=73)
Percent of Patients
0.0
0.1
0.2
0.3
0.4
0.5
1
3
4
5
6
7
8
3–month GOS–E score
Wilcoxon Rank Sum Test: W=19074 , p=0.01


TRACK–TBI, 18–65yrs, GCS 13–15, by MRI Contusion (Neuroradiologist 2
MRI Contusion=No (n=442)
MRI Contusion=Yes (n=75)
Percent of Patients
0.0
0.1
0.2
0.3
0.4
0.5
1
3
4
5
6
7
8
3–month GOS–E score
Wilcoxon Rank Sum Test: W=18881.5 , p=0.042


TRACK–TBI, 18–65yrs, GCS 13–15, by MRI Contusion (Neuroradiologist 3
MRI Contusion=No (n=442)
MRI Contusion=Yes (n=75)
Percent of Patients
0.0
0.1
0.2
0.3
0.4
0.5
1
3
4
5
6
7
8
3–month GOS–E score
Wilcoxon Rank Sum Test: W=19282 , p=0.017







Interrater reliability (IRR) Study Overview

The percent agreement (PA), positive percent agreement (PPA), and negative percent agreement (NPA) were determined for each pair of board certified neuroradiologists who participated in the IRR study. The average of the pairwise measure over the three readers were calculated (APA = Average Percent Agreement, ANA = Average Negative Agreement). In addition, the 95% confidence intervals for each measure were calculated using a bootstrap procedure. Based on the results of the biomarker-outcome association study, only the IRR results for contusions are provided.

Study population

The study patient population is the same as the biomarker-outcome association study. All readers were U.S. board-certified neuroradiologists.

Results of IRR for contusion

	Reader 1 vs Reader 2	Reader 2 vs Reader 3	Reader 1 vs Reader 3
PPA [95% CI]	86.7% [76.8-93.4%]	86.7% [76.8-93.4%]	88.0% [78.4-94.4%]
NPA [95% CI]	98.2% [96.5-99.2%]	97.7% [95.9-98.9%]	98.4% [96.8-99.4%]
PA [95% CI]	96.5% [95.0-98.15%]	96.1% [94.4-97.7%]	96.9% [95.4-98.3%]

	Reader 2 vs Reader 1	Reader 3 vs Reader 2	Reader 3 vs Reader 1
PPA [95% CI]	89.0% [79.5-95.1%]	86.7% [76.8-93.4%]	90.4% [81.2-96.1%]
NPA [95% CI]	97.7% [95.9-98.9 %]	97.7% [95.9-98.9%]	98.0% [96.2-99.1%]
PA [95% CI]	96.5% [95.0-98.15%]	96.9% [95.4-98.3%]	96.1% [94.4-97.7%]

	Reader 1 vs Reader 2	Reader 2 vs Reader 3	Reader 1 vs Reader 3
APA [95% CI]	87.8% [81.5-92.6%]	86.7% [80.2-91.7%]	89.2% [83.0-93.7%]
ANA [95% CI]	98.0% [96.8-98.8%]	97.7% [96.5-98.6%]	98.2% [97.1-99.0%]

ADDITIONAL EVIDENCE TO SUPPORT QUALIFICATION

In a previous investigation[2], the requestor studied the relationship between TBI-CDE defined pathoanatomic injuries identified on MRI and the outcomes of mild TBI (mTBI) patients at 3 months post injury. The results showed that one or more brain contusions and ≥4 foci of hemorrhagic axonal injuries were independently correlated with poorer 3-month patient outcome when demographic/socioeconomic, clinical and CT findings were controlled. As part of this MDDT submission, the requestors carried out a prospective study with three neuroradiologists to independently validate the initial results. This prospective study, as described under the *Summary of Evidence to Support Qualification,* was reviewed as part of the qualification package for this MDDT.

ASSESSMENT OF ADVANTAGES/DISADVANTAGES OF QUALIFICATION

Assessments of Advantages of Using the MDDT

Use of this tool may serve as an option in the design of clinical trials which help advance the study of mTBI. While researchers may choose to select other criteria to enrich a clinical trial, the tool proposed here may serve as a convenient methodology for patient selection to enrich the patient population to either (1) decrease the overall number of subjects needed in the trial or (2) increase the likelihood of observing a statistically significant treatment effect in a trial of similar number of patients.

Below is a hypothetical example of how the MDDT can be used as part of the evaluation of a medical device. The values used in this example are based on the results of the clinical study reviewed as part of the qualification. The company name, "CureForPCS" is fictional.

CureForPCS has developed a therapy for postconcussive syndrome (PCS), and has an estimated effect size for its therapy based on early-phase clinical trials. It plans to conduct a clinical trial to demonstrate the therapy's effectiveness in mild traumatic brain injury (GCS 13-15).

To boost the power for detecting a statistically significant treatment effect, the company decides to enrich their study population with patients expected to have poorer functional outcome, and thus for whom therapy could be shown to have a benefit. Based on biomarker-outcome association study data, patients with brain contusion on MRI are more likely (71.8%) than those without (54.8%) to have poor outcome, defined as a Glasgow Outcome Scale – Extended (GOS-E) of ≤7 at 3 months postinjury. Given that 14.4% of mild TBI patients in the biomarker-outcome association study demonstrated brain contusion on MRI, the percent of patients expected to have a poor outcome without regard to the presence of a brain contusion is 57.3%.

	Biomarker Positive Only (at 3 months)		Biomarker Negative Only (at 3 months)		Intended Population (All Patients at 3 months)	
	GOS-E ≤ 7	GOS-E = 8	GOS-E ≤ 7	GOS-E = 8	GOS-E ≤ 7	GOS-E = 8
Reader 1	72.6% (53/73)	27.4% (20/73)	54.7% (243/444)	45.3% (201/444)	57.3% (296/517)	42.7% (221/517)
Reader 2	70.7% (53/75)	29.3% (22/75)	55.0% (243/442)	45.0% (199/442)	57.3% (296/517)	42.7% (221/517)
Reader 3	72.0% (54/75)	28.0% (21/75)	54.8% (242/442)	45.2% (200/442)	57.3% (296/517)	42.7% (221/517)

- Proportion of biomarker-positive patients who have GOS-E≤7 at 3 months, averaged across all 3 readers: 71.8%
- Proportion of biomarker-negative patients who have GOS-E≤7 at 3 months, averaged across all 3 readers: 54.8%
- Proportion of all patients (regardless of biomarker) who have GOS-E≤7 at 3 months, averaged across all 3 readers: 57.3%
- Prevalence of contusion on brain MRI, averaged across all 3 readers: 14.4%

Applying this information, the company uses the MDDT to enroll a study population in which 50% of the subjects have brain contusion on MRI, and 50% do not. We would expect 63.3% (average of 54.8% and 71.8%) of this "enriched" population, without treatment, to have a GOS-E ≤7 at 3 months postinjury. The company decides to enroll 100 patients in its control arm, and

100 patients in its therapy arm. In this case, 63 patients of the 100-patient control group, and 63 of the 100-patient treatment group, would be expected, without treatment, to have a GOS-E ≤7 at 3 months postinjury.

Had the study population ***not*** been enriched for those with brain contusion on MRI, only 57 of the 100-patient control group, and 57 of the 100-patient treatment group would be expected, without treatment, to have a GOS-E of ≤7 at 3 months (based on prevalence).

Using the MDDT, the company tests its therapy in an "enriched" population – that is, a study population with a greater proportion of patients in whom the therapy could be proven to have a benefit. If the therapy were tested in a population with too few patients who could be shown to benefit from the treatment, this would reduce the power of the trial to prove a statistically significant treatment effect, or require a larger sample size.

Assessments of Disadvantages of Using the MDDT

The use of this tool requires participants in a study to have an MR exam which may require additional resources and potentially increase the number of screen failures for a future trial (individuals who might otherwise meet the eligibility for the trial but are not included based on the results of the biomarker test). This may mean that there will be added costs to the clinical trials through the requirement of a brain MRI and through the additional patients who would need to be screened due to some potential participants being excluded due to MRI contraindications.

Individuals using this tool should clearly understand the statistical limitations of the data provided to support this qualification and the uncertainty associated with the use of the MDDT. The users should carefully review the results presented in under *The Summary of Evidence to Support Qualification* and use this tool within its qualified Context of Use.

CONCLUSION

Prior investigations, possible advantages and disadvantages, as well as the prospective clinical trial information were all taken into considerations in the decision to qualify the MDDT as an enrichment tool.

REFERENCE

1. NINDS COMMON DATA ELEMENTS. HTTPS://COMMONDATAELEMENTS.NINDS.NIH.GOV/TBI.ASPX#TAB=DATA_STANDARDS

2. Yuh, Esther L., et al. "Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury." *Annals of neurology* 73.2 (2013): 224-235.

3. Yue, John K., et al. "Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury." *Journal of neurotrauma* 30.22 (2013): 1831-1844.

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