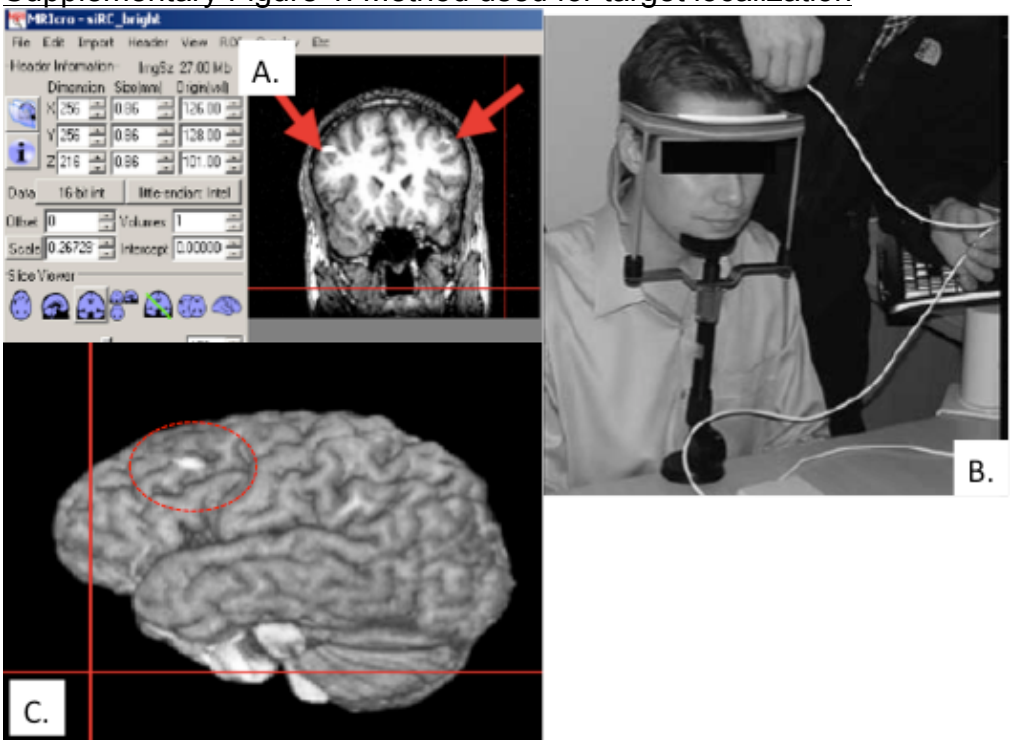
Supplementary Materials

Content:

Detailed description of target site localization using individualized neuronavigation:

Target site localization was performed prior to the start of the first rTMS treatment session using a previously published method developed in house (12). A pre-selected DLPFC coordinate (MNI coordinate (x,y,z) left: -50, 30, 36mm; right: +50, 30, 36) corresponding to juncture of BA 9 and 46 was superimposed on the participant's normalized MRI using the following steps (12). First, the best non-linear transformation for each participant was used to convert standard space coordinates for left and right DLPFC to the cortex (using spm_normalize from SPM2 run under MATLAB, The MathWorks, Inc. Natick, MA) following manual input of the native space anterior commissure coordinate. Next, a marching cube algorithm was used to create a triangular mesh wrapping the iso-surface of the scalp. The optimal scalp position for targeting the DLPFC was determined based on localization of a vertex of triangular mesh with a perpendicular that passes through the DLPFC on the cortex (12). With the position of the DLPFC target site superimposed on the participant's normalized MR image (see supplementary Figure 1A), neuronavigation (using the MINIBIRD system; Ascension Technologies combined with MRIcro/reg package) was used to co-register the participant's normalized MRI with their real head geometry using the 7 fiducial markers on the participant's MRI as reference points. Prior to the first rTMS treatment session, the participant was asked to sit and position their head in a frame within the treatment suite. The MINIBIRD magnetic wand was then used to co-register each of the 7 fiducial landmark positions on the normalized MRI with the corresponding positions on the scalp using MRIreg (see supplementary Figure 1B included as published in (13). The reliability of the technique was confirmed by navigating the wand to each position on the scalp and confirming registration with landmarks on the image. Following successful co-registration, the image was skull-stripped with a bright spot corresponding to the target stimulation site superimposed on the cortex. The exact location on the participant's scalp corresponding to the bright spot on the MRI was then marked (using the magnetic wand to navigate the wand cursor onto the target site on the cortex) using MRIreg 'tracker' mode (supplementary Figure 1C). The marked spot was used for rTMS coil placement prior to the first rTMS treatment session and recorded for subsequent treatment sessions.

Supplementary Figure 1. Method used for target localization



**Supplementary Table 1:** Participant Reported Psychiatric Medications, Co-occurring Mental Health Conditions (Based on the MINI and Self Report) & Total Education Years

| Group | Total Sample (n=40) | *Sham (n=20)* | *Active (n=20)* |
|---|---|---|---|
| Any Psychotropic Medication | 26 (65%) | 10 (50%) | 16 (80%) |
| *SSRI* | 13 (32.5%) | 4 (20%) | 9 (45%) |
| *SNRI* | 2 (5%) | 1 (5%) | 1 (5%) |
| *Tetracyclic Antidepressant* | 2 (5%) | 1 (5%) | 1 (5%) |
| *NDRI* | 3 (7.5%) | 2 (10%) | 1 (5%) |
| *Atypical Antipsychotic* | 8 (20%) | 3 (15%) | 5 (5%) |
| *Amphetamine* | 2 (5%) | 0 | 2 (10%) |
| *Methylphenidate* | 7 (17.5%) | 2 (10%) | 5 (25%) |
| *Benzodiazepine (≤2mg Lorazepam/day)* | 4 (10%) | 1 (5%) | 3 (15%) |
| *Medical Marijuana* | 1 (2.5%) | 0 | 1 (5%) |
| **Comorbidity on MINI** | 25 (62.5%) | 11 (55%) | 14 (70%) |
| *Major Depressive Episode (Current)* | *10 (25%)* | *7 (35%)* | *3 (15%)* |
| *Dysthymia* | *1 (2.5%)* | *0* | *1 (5%)* |
| *Suicide Risk Present* | *18 (45%)* | *9 (45%)* | *9 (45%)* |
| *Hypomanic Episode (Current)* | *1 (2.5%)* | *1 (5%)* | *0* |
| *Hypomanic Episode (Past)* | *6 (15%)* | *3 (15%)* | *3 (15%)* |
| *Panic Disorder (Current)* | *2 (5%)* | | |
| *Panic Disorder (Lifetime)* | *3 (7.5%)* | *1 (5%)* | *2 (10%)* |
| *Limited Symptoms Panic Disorder (Lifetime)* | *3 (7.5%)* | *1 (5%)* | *2 (10%)* |
| *Agoraphobia* | *5 (12.5%)* | *2 (10%)* | *3 (15%)* |
| *Social Phobia* | *3 (7.5%)* | *3 (15%)* | *0* |
| *Obsessive Compulsive Disorder* | *4 (10%)* | *3 (15%)* | *1 (5%)* |
| *Psychotic Disorder (lifetime)* | *3 (7.5%)* | *2 (10%)* | *1 (5%)* |
| *Psychotic Disorder (current)* | *3 (7.5%)* | *2 (10%)* | *1 (5%)* |
| *Mood Disorder with Psychotic Features* | *2 (5%)* | *1 (5%)* | *1 (5%)* |
| *Generalized Anxiety Disorder* | *10 (25%)* | *4 (20%)* | *6 (30%)* |
| *Anorexia Nervosa* | *1 (2.5%)* | *1 (5%)* | *0* |

| | | | |
|---|---|---|---|
| *Antisocial Personality Disorder* | *1 (2.5%)* | *0* | *1 (5%)* |
| **Self-Reported Diagnoses** | | | |
| *Anxiety Disorder* | 5 (12.5%) | 3 (15%) | 2 (10%) |
| *ADHD* | 8 (20%) | 3 (15%) | 5 (25%) |
| *Depression* | 6 (15%) | 2 (10%) | 4 (20%) |
| *Obsessive-Compulsive Disorder* | 4 (10%) | 3 (15%) | 1 (5%) |
| *Schizophrenia or other psychotic disorder* | 1 (2.5%) | 1 (5%) | 0 |
| *Bipolar Disorder* | 3 (7.5%) | 1 (5%) | 2 (10%) |
| *Post-Traumatic Stress Disorder* | 1 (2.5%) | 0 | 1 (5%) |
| *Tourette Syndrome* | 2 (5%) | 2 (10%) | 0 |
| *Learning Disorder* | 2 (5%) | 1 (5%) | 1 (5%) |
| Years of Completed Education[a] | 13.8±2.8 | 12.8±2.3 | 15±2.9 |
| Educational Attainment | | | |
| *Grade 7-12 Only* | 7 (17.5%) | 6 (30%) | 1 (5%) |
| *High School Only* | 11 (27.5%) | 6 (30%) | 5 (25%) |
| *Some-Post Secondary* | 16 (40%) | 6 (30%) | 10 (50%) |
| *Completed 2yr Program* | 2 (5%) | 2 (10%) | 2 (10%) |
| *Completed 4yr Program* | 3 (7.5%) | 0 | 1 (5%) |
| *Some Graduate School* | 1 (2.5%) | 0 | 1 (5%) |
| *Completed Graduate School* | 0 | 0 | 0 |

MINI=The Mini International Neuropsychiatric Interview

[a]Years of completed education calculated as total number of education years completed starting from grade 1 (e.g., currently in second year undergraduate university degree=13, grades 1-12 + 1 additional undergraduate year).

Supplementary Table 2: Baseline Clinical & Cognitive Characteristics Presented By Gender

| **Group** | Total Group Females (N=12) | Total Group Males (N=28) | Females, Sham Group (n=6) | Females, Active Group (n=6) |
|---|---|---|---|---|
| Age in years | 22.58 ± 4.7 | 22.57 ±4.5 | 20.17 ± 4.6 | 25.00 ± 3.6 |
| Any Psychotropic Medication | 8 (83.3%) | 18 (64.3%) | 3 (50%) | 5 (83.3%) |
| Inclusion IQ[a] | 111.2±18.7[a] | 109.1±17.3 | 113.83 ± 23.4 | 108.50 ± 14.5 |
| Comorbidity on MINI | 11 (91.7%) | 14 (50%) | 5 (83.3%) | 6 (100%) |
| Years of Completed Education[b] | 13.92 ± 3.1 | 13.82 ± 2.8 | 11.67 ± 0.8 | 16.17 ± 2.8 |
| *VABS-II* Adaptive Behavior Composite | 75.2±12.3 | 74.2±9.9 | 76.67 ± 14.4 | 73.67 ±11.2 |
| *BRIEF* Metacognition Index | 71.7±9.0 | 70.8±10.2 | 75.17 ± 8.8 | 77.00 ±7.7 |
| BRIEF Global Executive Composite | 73.33 ± 9.4 | 67.61 ± 8.7 | 71.33 ± 10.4 | 75.33 ± 8.8 |
| *CANTAB* SWM (total errors) | 27.2±19.2 | 21.5±20.1 | 28.83 ± 21.2 | 25.50 ± 18.8 |
| SWM (strategy) | 30.50 ± 7.4 | 29.64 ± 6.9 | 32.00 ± 7.3 | 29.00 ± 7.9 |

All values presented as Mean ±SD

[a]Inclusion IQ= General Abilities Index of the Wechsler Adult Intelligence Scale-Fourth Edition, MINI=The Mini International Neuropsychiatric Interview, VABS-II= Vineland Adaptive Behavior Scale-II, BRIEF= Behavioral Rating Inventory for Executive Function, CANTAB=The Cambridge Neuropsychological Test Automated Battery, SWM=spatial working memory

[b]Years of completed education calculated as total number of education years completed starting from grade 1 (e.g., currently in second year undergraduate university degree=13, grades 1-12 + 1 additional undergraduate year).

Supplementary Figure 2:
Comparison of cognitive performance in participants with ASD and ASD plus attention-deficit/hyperactivity disorder (ADHD)

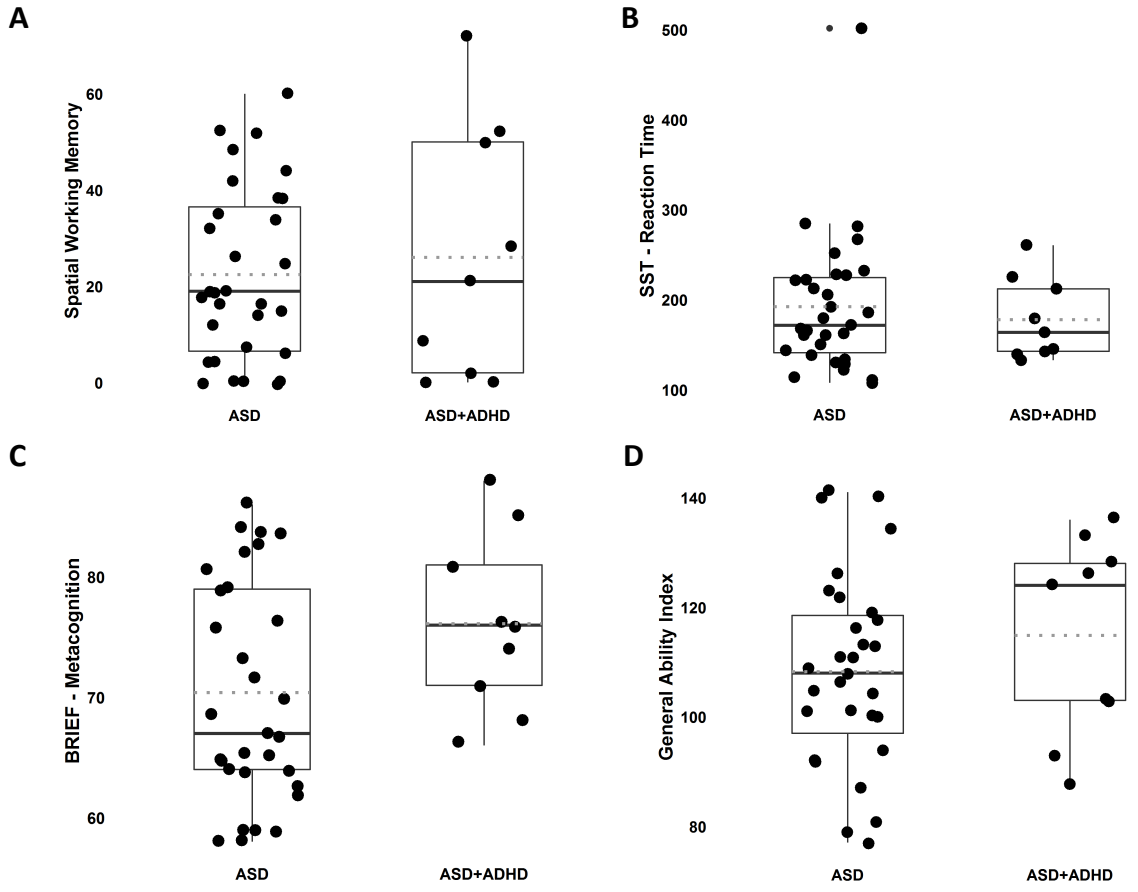
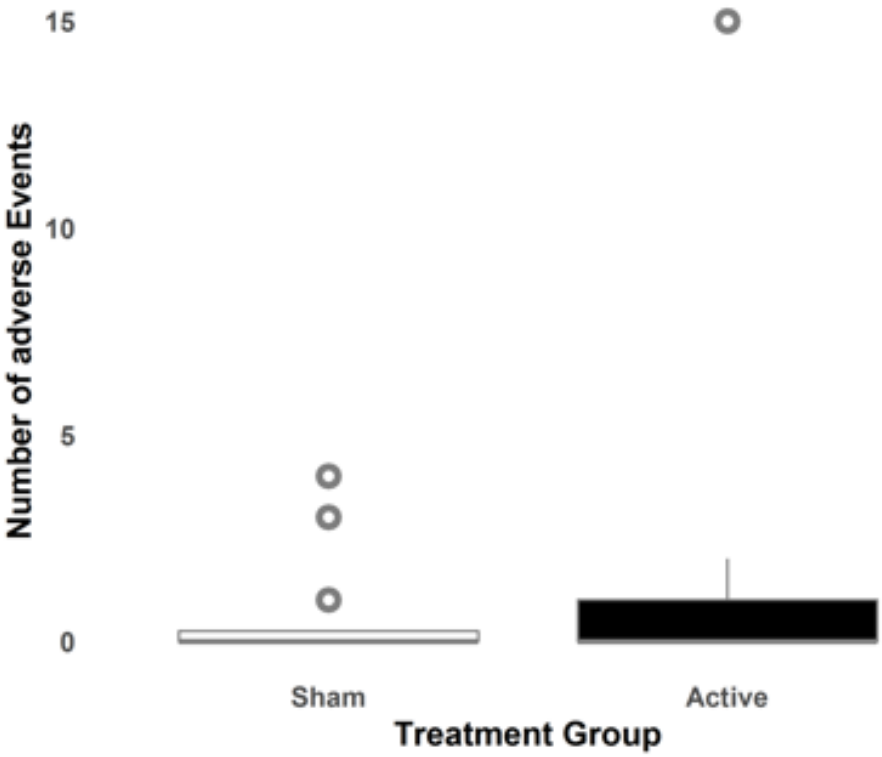



Figure 1 provides a visual comparison of performance on different cognitive measures in participants with ASD+ADHD that participated in the current trial. A total of 9/40 (~23%) clinical trial participants had clinically significant ADHD, which was defined as being treated with a stimulant medication at the time of trial participation. Means (dotted line), means (solid line) and standard deviations for ASD+ADHD trial participants compared to all other trial participants are provided for: 1A) The Cambridge Neuropsychological Test Automated Battery (CANTAB) spatial working memory total errors, (1B) CANTAB stop signal reaction time (SST-Reaction Time), (1C) the Behavioral Rating Inventory for Executive Function (BRIEF) metacognition index, and (1D) general intellectual ability (i.e., general ability index on the Wechsler Adult Intelligence Scale-Fourth Edition). Although the subgroup with ASD+ADHD is small, EF scores overlap across ASD and ASD+ADHD participants without clear indication of a distinction between groups.

Supplementary Figure 3. Total number of adverse events experienced by group



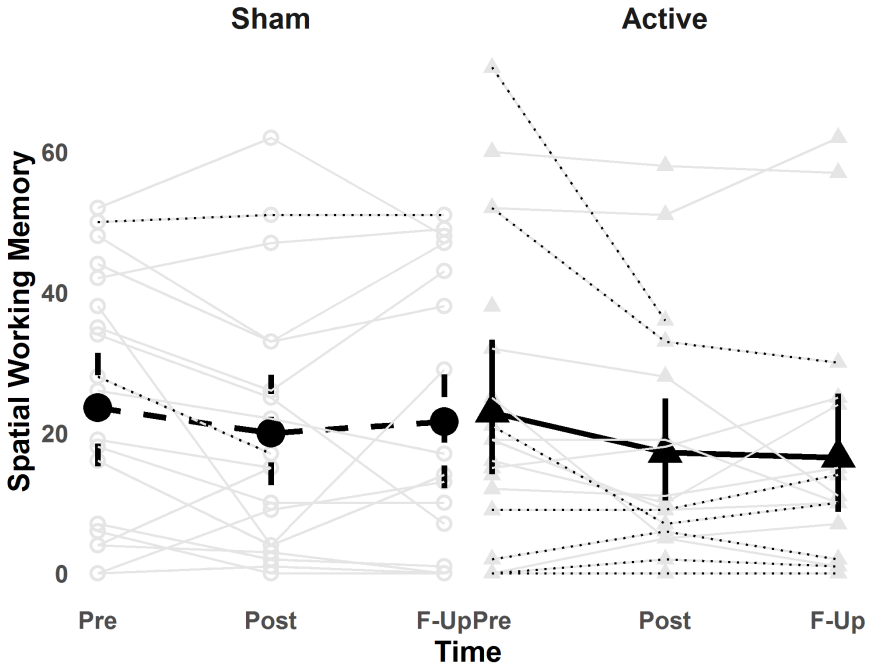

The rate of adverse events in the active group was 1.37 times the rate in the sham group (rate: active=7%, sham=~2.6%, p-value= 0.24; p=0.9, after exclusion of one participant in active group that reported 15 adverse events

Supplementary Table 3. Total number of events reported by type presented for each group

| | Sham | | Active | |
|---|---|---|---|---|
| Adverse Event | **n** | **%** | **n** | **%** |
| Headache | 5 | 50.0% | 17 | 73.9% |
| Pain at application site | 1 | 10.0% | 1 | 4.3% |
| Neck pain | 0 | 0.0% | 1 | 4.3% |
| Nose bleed | 2 | 20.0% | 0 | 0.0% |
| Nausea | 0 | 0.0% | 1 | 4.3% |
| Laceration | 1 | 10.0% | 0 | 0.0% |
| Congestion | 0 | 0.0% | 1 | 4.3% |
| Other | 1 | 10.0% | 2 | 8.7% |
| **Total events reported** | **10** | **100.0%** | **23** | **100.0%** |

**Note: A number of participants that reported any adverse event reported more than one event over the treatment course.**

Supplementary Figure 4. Change in spatial working memory performance in active and sham rTMS groups across baseline (Pre: n=20 active, n=20 sham), post rTMS (Post: n=18 active, n=20 sham) and one-month follow-up (F-Up: n=17 active, n=17 sham) time-points with individuals with ASD plus ADHD demarcated by dotted lines.




Spatial working memory=total number of errors on the spatial working memory test from the
Cambridge Neuropsychological Test Automated Battery (CANTAB)

| PROTOCOL NO.:<br><br>PROTOCOL TITLE: | **SUBJECT ID:**<br><br>EF- ☐ ☐ ☐ | camh Temerty Centre for Therapeutic Brain Intervention<br>Temerty Centre for Therapeutic Brain Intervention<br>**Centre for Addiction and Mental Health** |
|---|---|---|

***ALLERGY:** _____ **Stimulation intensity: 90%**

**Motor Threshold: R:** _____**%** **L:** _____ **%** **Randomization ID:** _____

**Stimulation Intensity: R:** _____**%** **L:** _____**%**

## Treatment 1

Treatment was performed as scheduled: ☐ **Yes** ☐ **No** *If no, specify reason:* _____

Date of treatment: _____/_____/_____
(DD/MMM/YYYY)

Treatment interrupted: ☐ **Yes** ☐ **No** **If yes, specify reason:** ☐ Coil overheat ☐ Coil repositioning
☐ System/power shut down
☐ Earplugs fell out
☐ Other: _____

Comments: _____

_____

_____

**Were adverse events or physical discomforts reported by the patient since the last treatment or during the current treatment?** ☐ **Yes** ☐ **No** **If "YES", please fill in the ADVERSE EVENTS FORM**

**Has your medication schedule changed?** ☐ **Yes** ☐ **No**

**Do you believe you have received the active or the sham treatment?** _____

**How confident are you that you have received active or sham?**

1 2 3 4 5 6 7 8 9 10

**1-Not at all confident** **10- Extremely confident**

| | Name of medication | Dosage | Indication |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |

**Pain/Discomfort Scale: 1-10**

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

**1-No pain** **10- Worst pain**

**Operator Name:** _____

**Date of signature:** _____/_____/_____ (DD/MMM/YYYY)

**Operator signature:** _____

PROTOCOL NO:

PROTOCOL TITLE:

PARTICIPANT ID:

_____ – _____ _____ _____

camh Temerty Centre for Therapeutic Brain Intervention

**Centre for Addiction and Mental Health**

# Adverse Events Form

| | Adverse Event Reported Date (DD-MMM-YYYY) | Visit # | Adverse Event Description (MedDRA preferred term) | Event Start Date (DD-MM-YYYY) | Event End Date (DD-MM-YYYY) | Reported as SAE? | Relation | Severity | Action | Outcome | Comments | PI's Initials |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | | | | | | | | | | | | |
| 2. | | | | | | | | | | | | |
| 3. | | | | | | | | | | | | |
| 4. | | | | | | | | | | | | |

| Reported as SAE? | Relation to Study Device | Severity (Grade) | Action | | Outcome | |
|---|---|---|---|---|---|---|
| 0 = No<br>1 = Yes<br>If Yes, complete CAMH SAE form and submit to REB | 1 = Not related<br>2 = Probably not related<br>3 = Possibly related<br>4 = Most probably related | 1 = Mild<br>2 = Moderate<br>3 = Severe | 1 = No treatment<br>2 = Treatment with medication<br>3 = Treatment other (please specify in comments)<br>4 = Hospitalization | 5 = CPR<br>6 = Other (please specify in comments) | 1 = Resolved<br>2 = Resolving<br>3 = Not resolved<br>4 = Resolved with sequelae | 5 = Fatal<br>6 = Unknown |

Investigator name:

Date of Signature:

DD - MMM - YYYY

Investigator signature: