

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): a randomized, double blind, parallel-arm, placebo-controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020316
Article Type:	Protocol
Date Submitted by the Author:	30-Oct-2017
Complete List of Authors:	<p>Shelton, Kenneth; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Qu, Jason; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Bilotta, Federico; University of Rome "Sapienza", Anesthesiology</p> <p>Brown, Emery; Massachusetts Institute of Technology Institute for Medical Engineering and Science; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Cudemus, Gaston; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>D'Alessandro, David; Massachusetts General Hospital, Department of Surgery, Division of Cardiac Surgery</p> <p>Deng, Hao; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>DiBiasio, Alan; Massachusetts General Hospital, Department of Pharmacy</p> <p>Hahn, Eunice; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Hobbs, Lauren; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Houle, Timothy T. ; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Ibala, Reine; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Loggia, Marco; Massachusetts General Hospital, Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology</p> <p>Pavone, Kara; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Shaefi, Shahzad; Beth Israel Deaconess Medical Center, Department of Anesthesia and Critical Care</p> <p>Tolis, George; Massachusetts General Hospital, Department of Surgery, Division of Cardiac Surgery</p> <p>Westover, Brandon; Massachusetts General Hospital, Department of Neurology</p> <p>Akeju, Oluwaseun; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p>
Keywords:	Delirium, Biomimetic sleep, Dexmedetomidine, Cardiac surgery < SURGERY, Patient reported outcomes

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

SCHOLARONE™  
Manuscripts

For peer review only

1  
2  
3 **Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep**  
4 **(MINDDS): a randomized, double blind, parallel-arm, placebo-controlled trial**  
5  
6  
7

8 KT Shelton<sup>1</sup>, J Qu<sup>1</sup>, F Bilotta<sup>2</sup>, EN Brown<sup>1,3</sup>, G Cudemus<sup>1</sup>, DA D'Alessandro<sup>4</sup>, H Deng<sup>1</sup>, A  
9 DiBiasio<sup>5</sup>, EY Hahm<sup>1</sup>, LE Hobbs<sup>1</sup>, TT Houle<sup>1</sup>, R Ibalá<sup>1</sup>, M Loggia<sup>6</sup>, KJ Pavone<sup>1</sup>, S Shaefi<sup>7</sup>, G  
10 Tolis<sup>4</sup>, MB Westover, O Akeju\*<sup>1</sup>

11 **Affiliations:**

12 <sup>1</sup> Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General  
13 Hospital, Boston MA, 02114

14 <sup>2</sup> Department of Anaesthesia and Critical Care Medicine, "Sapienza" University Rome

15 <sup>3</sup> Institute for Medical Engineering and Sciences, Massachusetts Institute of Technology,  
16 Cambridge MA, 02139

17 <sup>4</sup> Department of Surgery, Division of Cardiac Surgery, Massachusetts General Hospital, Boston  
18 MA, 02114

19 <sup>5</sup> Department of Pharmacy, Massachusetts General Hospital, Boston MA, 02114

20 <sup>6</sup> Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology,  
21 Massachusetts General Hospital, Boston MA, 02114

22 <sup>7</sup> Department of Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, Boston  
23 MA, 02215

24 <sup>8</sup> Department of Neurology, Massachusetts General Hospital, Boston MA, 02114  
25  
26  
27  
28  
29

30 \*To whom correspondence should be addressed

31 Oluwaseun Johnson-Akeju

32 Massachusetts General Hospital

33 Department of Anesthesia, Critical Care and Pain Medicine

34 55 Fruit St

35 Boston, MA 02114

36 USA

37 oluwaseun.akeju@mgh.harvard.edu  
38  
39  
40  
41  
42  
43

44 **Version:** October 15, 2017

45 **Amendment 1:**

46 NCT02856594

47 Funding for the MINDDS trial is through a grant awarded by the National Institutes on Aging  
48 (R01 AG053582).  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59  
60

**STUDY TEAM ROSTER****Principal****Investigator:****Oluwaseun Johnson-Akeju, M.D., M.M.Sc.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-724-2000  
oluwaseun.akeju@mgh.harvard.edu

**Co-Investigators:****Federico Bilotta, MD**

University of Rome 'La Sapienza'  
Department of Anesthesiology  
Piazzale Aldo Moro,  
5, 00185 Roma, Italy  
339 33 708 22  
bilotta@tiscali.it

**Emery N. Brown, M.D., Ph.D.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-324-1880  
enb@neurostat.mit.edu

**Gaston Cudemus, M.D.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-726-9149  
gcudemus@mgh.harvard.edu

**David D'Alessandro, M.D.**

Massachusetts General Hospital

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 Department of Surgery  
4 Division of Cardiac Surgery  
5 Cox Building 644  
6 Boston, MA 02114  
7 United States  
8 617-726-8841  
9 dadalessandro@mgh.harvard.edu  
10  
11

12  
13 **Hao Deng, M.D., M.P.H.**  
14 Massachusetts General Hospital  
15 Department of Anesthesiology  
16 55 Fruit Street  
17 Gray/Jackson 444  
18 Boston, MA 02114  
19 United States  
20 617-643-6757  
21 hdeng1@mgh.harvard.edu  
22  
23

24 **Alan DiBiasio, B.S. Pharm**  
25 Massachusetts General Hospital  
26 Department of Pharmacy,  
27 55 Fruit St  
28 Gray/Bigelow 005  
29 Boston, MA 02114  
30 United States  
31 617-724-1270  
32 adibiasio@partners.org  
33  
34  
35

36 **Eunice Y Hahm, B.S**  
37 Massachusetts General Hospital  
38 Department of Anesthesiology  
39 55 Fruit Street  
40 Gray/Jackson 444  
41 Boston, MA 02114  
42 United States  
43 617-724-2000  
44 ehahm@mgh.harvard.edu  
45  
46  
47

48 **Lauren E. Hobbs, M.S.**  
49 Massachusetts General Hospital  
50 Department of Anesthesiology  
51 55 Fruit Street  
52 Gray/Jackson 444  
53 Boston, MA 02114  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

1  
2  
3 United States  
4 617-724-9857  
5 lehobbs@mgh.harvard.edu  
6

7  
8 **Timothy Houle, Ph.D.**

9 Massachusetts General Hospital  
10 Department of Anesthesiology  
11 55 Fruit Street  
12 Gray/Jackson 444  
13 Boston, MA 02114  
14 United States  
15 617-724-2111  
16 thoule1@mgh.harvard.edu  
17

18 **Reine Ibala, B.S.**

19 Massachusetts General Hospital  
20 Department of Anesthesiology  
21 55 Fruit Street  
22 Gray/Jackson 444  
23 Boston, MA 02114  
24 United States  
25 617-724-2000  
26 ribala@mgh.harvard  
27

28 **Marco L. Loggia, Ph.D.**

29 Massachusetts General Hospital  
30 Department of Radiology  
31 149 13th Street  
32 CNY - Building 149  
33 Charlestown, MA 02129  
34 United States  
35 617-643-7267  
36 marco.loggia@mgh.harvard.edu  
37

38  
39 **Jason Qu, M.D.**

40 Massachusetts General Hospital  
41 Department of Anesthesiology  
42 55 Fruit Street  
43 Gray/Jackson 444  
44 Boston, MA 02114  
45 United States  
46 617-643-4401  
47 jqu@partners.org  
48  
49

50 **Kara J. Pavone, B.S., B.S.N., R.N.**

51 Massachusetts General Hospital  
52 Department of Anesthesiology  
53 55 Fruit Street  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

1  
2  
3 Gray/Jackson 444  
4 Boston, MA 02114  
5 United States  
6 617-724-9857  
7 kpavone@mgh.harvard.edu

8 **Shahzad Shaefi, M.D., MPH**

9 Beth Israel Deaconess Medical Center  
10 Department of Anesthesia and Critical Care  
11 330 Brookline Avenue,  
12 Feldberg 407  
13 Boston, MA 02215  
14 United States  
15 617-667-3112  
16 sshaeft@bidmc.harvard.edu  
17  
18

19 **Kenneth Shelton, M.D.**

20 Massachusetts General Hospital  
21 Department of Anesthesiology  
22 55 Fruit Street  
23 Gray/Jackson 444  
24 Boston, MA 02114  
25 United States  
26 617-726-0917  
27 kshelton2@partners.org  
28  
29  
30

31 **George Tolis, M.D.**

32 Massachusetts General Hospital  
33 Department of Surgery  
34 Division of Cardiac Surgery  
35 55 Fruit Street  
36 Cox Building 654  
37 Boston, MA 02114  
38 United States  
39 617-643-9280  
40 gtolis@partners.org  
41  
42  
43  
44

45 **M. Brandon Westover, MD, PhD**

46 Massachusetts General Hospital  
47 Department of Neurology  
48 55 Fruit Street  
49 Boston, MA 02114  
50 United States  
51 617-726-3311  
52 mwestover@mgh.harvard.edu  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

<b>Primary Registry and Trial Identifying Number</b>	<b>ClinicalTrials: NCT02856594</b>
<b>Date of Registration</b>	July 29 2016
<b>Secondary Identifying Numbers</b>	IRB ID#: 2016 P000742
<b>Source(s) of Monetary Support</b>	National Institute on Aging Grant (Award Reference Number R01 AG053582-01)
<b>Primary Sponsor</b>	Department of Anesthesiology, Critical care and Pain Medicine Massachusetts General Hospital Boston, MA 02114
<b>Contact name</b>	Oluwaseun Akeju, M.D., M.M.Sc oluwaseun.akeju@mgh.harvard.edu 617-724-2000 Department of Anesthesiology, Critical care and Pain Medicine Massachusetts General Hospital 55 Fruit Street Gray/Jackson 444 Boston, MA 02114 United States
<b>Contact for Scientific Queries</b>	Oluwaseun Akeju, M.D., M.M.Sc oluwaseun.akeju@mgh.harvard.edu 617-724-2000 Department of Anesthesiology Massachusetts General Hospital 55 Fruit Street Gray/Jackson 444 Boston, MA 02114 United States
<b>Public Title</b>	Protocol for the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) Trial
<b>Scientific Title</b>	Protocol for the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) Trial: a Randomized, Double blind, Parallel-

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1		
2		
3		arm, Placebo-controlled Clinical Trial
4		
5	<b>Countries of Recruitment</b>	United States
6		
7	<b>Health Condition(s) or Problem(s) Studied</b>	Postoperative delirium, predictors of delirium
8		
9		
10		
11	<b>Intervention(s)</b>	Trial arm 1: Dexmedetomidine-induced Sleep Group
12		(primary intervention)
13		Post cardiac surgical patients admitted to the cardiac
14		surgical intensive care unit (CSICU) and extubated at
15		least 30 minutes prior to 8:30 PM would receive a
16		sleep induction dose of dexmedetomidine (1mcg/kg
17		over 40 minutes; maximum administered dose of
18		80mcg) at 9 PM every night throughout their CSICU
19		stay. Trial patients admitted to the CSICU and
20		extubated after 8:30 PM, but before 2 AM, would
21		receive a sleep induction dose of dexmedetomidine
22		within 30 minutes of extubation. However, throughout
23		the rest of the CSICU stay the dexmedetomidine
24		administration time will be targeted for 9 PM. Trial
25		patients admitted to the CSICU and remain intubated
26		past 2 AM will begin trial procedures the following day,
27		assuming they are extubated within 12 hours of
28		admission to the CSICU.
29		
30		
31		
32		
33		
34		Trial arm 2: Placebo Control Group.
35		Post cardiac surgical patients admitted to the CSICU
36		and extubated at least 30 minutes prior to 8:30 PM
37		would receive placebo (intravenous normal saline over
38		40 minutes) at 9 PM every night throughout their
39		CSICU stay. Trial patients admitted to the CSICU and
40		extubated after 8:30 PM, but before 2 AM, would
41		receive the placebo infusion of normal saline within 30
42		minutes of extubation. However, throughout the rest of
43		the CSICU stay the placebo administration time will be
44		targeted for 9 PM. Trial patients who are admitted to
45		the CSICU and remain intubated past 2 AM will begin
46		trial procedures the following day, assuming they are
47		extubated within 12 hours of admission to the CSICU.
48		
49		
50		
51		
52	<b>Key Inclusion, Exclusion and Objective Drop Criteria</b>	Inclusion Criteria
53		1. Age $\geq$ 60
54		

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for  $\geq 24$  hours
3. Scheduled same day surgical admission

#### Exclusion Criteria

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score  $> 5$
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit due to structural or anoxic brain damage
9. Surgical procedures requiring total circulatory arrest

#### Objective Drop Criteria

1. Surgical procedure scheduled as second case of the day, and/or to be commenced after 12pm
2. Scheduled for a second surgical procedure during hospital stay
3. Post-operative intubation  $> 12$  hours

#### **Trial Type**

Interventional  
 Allocation: Randomized  
 Intervention model: Parallel assignment  
 Blinding: Clinicians blinded to intervention, subject blinded to intervention, primary outcome assessor blinded to intervention  
 Assignment: Parallel  
 Primary purpose: Prevention

#### **Date of First Enrollment**

March, 2017

#### **Target Sample Size**

Recruiting until 300 patients receive the study

CONFIDENTIAL: This document is the intellectual property the MINDDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 intervention on Post Operative Day 0.  
4

5 **Recruitment Status** Enrolling  
6  
7

8 **Primary Outcome(s)** Outcome name: Incidence of postoperative delirium  
9

10 Method of measurement: The Long Confusion  
11 Assessment Method  
12

13 Time points of interest: Postoperative day 1  
14

15 **Key Secondary Outcomes**

16 Outcome name: ICU and hospital delirium/coma-  
17 free days  
18

19 Method of measurement: Delirium assessment with:  
20 The Long Confusion Assessment Method  
21

22 Time points of interest: Up until postoperative day 3,  
23 or up until postoperative day 7 or discharge for  
24 patients who are delirious beyond postoperative day  
25 5  
26  
27

28 Outcome name: Severity of Delirium  
29

30 Method of measurement: The Long Confusion  
31 Assessment Method  
32

33 Time points of interest: Up until postoperative day 3  
34 or up until postoperative day 7 for patients who are  
35 delirious beyond postoperative day 5  
36  
37

38 Outcome name: Date of Hospital Discharge /  
39 Length of Hospital Stay  
40

41 Method of measurement: Medical record review  
42

43 Time points of interest: Up till hospital discharge  
44

45 Outcome name: 30-day, 90-day, and 180-day  
46 mortality  
47

48 Method of measurement: Medical record review  
49

50 Time points of interest: 30 days, 90 days and 180  
51 days postoperatively  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

1  
2  
3 Outcome name: Postoperative cognitive status  
4

5 Method of measurement: Telephone Montreal  
6 Cognitive Assessment, 3D-CAM and PROMIS-29  
7 applied cognition abilities questionnaire  
8

9 Time points of interest: 30 days, 90 days and 180  
10 days postoperatively  
11

12 Outcome name: Postoperative health related quality  
13 of life  
14

15 Method of measurement: PROMIS-29 physical  
16 function, global health, pain interference  
17 questionnaires, and sleep questionnaire  
18

19 Time points of interest: 30 days, 90 days and 180  
20 days postoperatively  
21

22 Outcome name: Peri-operative EEG dynamics of  
23 delirium  
24

25 Method of measurement: Intraoperative and post-  
26 operative EEG  
27

28 Time points of interest: up to post-operative day 3  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

1  
2  
3 **Authors' contributions:** Authorship for this trial will be given to key personnel involved in trial  
4 design, recruitment, data collection, and data analysis. There are no publication restrictions and  
5 no professional writers will be involved in the generation of the manuscript. KTS, JQ, GC, HD,  
6 EYH, LEH, TTH, RI, KJP, and OA were responsible for conceptualizing trial design. JQ  
7 managed patient safety protocol. EYH, RI, and LH were responsible for recruitment, enrolment,  
8 and data collection. KTS, JQ, FB, ENB, GC, DAD, HD, AD, EYH, LEH, TTH, RI, ML, KJP, SS,  
9 GT, MBW, and OA have critically revised the MINDDS protocol and approved the final version.  
10 All authors agree to be accountable for the accuracy and integrity of all aspects of the MINDDS  
11 trial.  
12  
13  
14  
15  
16  
17

18 **Conflict of interest statement:** OA and ENB have a provisional patent application describing  
19 the use of alpha-2 agonists for promoting N3 sleep. All other authors have no interests to  
20 declare.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

## ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

### Principal Investigator:

Oluwaseun Akeju, M.D., M.M.Sc.

Responsibilities include: design and conduct of the MINDDS trial, preparation of protocol and revisions, organization of steering committee meetings, and publication of trial reports.

### Steering Committee:

Oluwaseun Akeju, M.D., M.M.Sc	Gaston Cudemus, M.D. Marco L Loggia, Ph.D.	Ken Shelton, M.D. Brandon M Westover, M.D., Ph.D.
Federico Bilotta, MD	Kara Pavone, B.SN., R.N	
Alan DiBiasio, Pharm.D	Jason Qu, M.D.	
Tim Houle, Ph.D	Shahzad Shaefi, M.D., MPH	

Responsibilities include: agreement of final protocol, reviewing progress of trial and if necessary, conducting changes to the protocol, coordinating with principal investigator, and communicating with trial management committee.

### Trial Management Committee:

Oluwaseun Akeju, M.D, M.M.Sc.  
Tim Houle, Ph.D.  
Lauren E Hobbs, M.S.  
Reine Ibala, B.S.  
Eunice Hahm, B.S.  
Kara Pavone, B.S.N, R.N.  
Jason Qu, M.D.  
Ken Shelton, M.D.

Responsibilities include: trial planning, organization of steering committee meetings, reporting SAEs (Serious Adverse Events) to Partners Healthcare IRB (Institutional Review Board), maintaining REDCap electronic database, reporting to steering committee, conducting data verification, recruitment, randomization, and follow-up of trial participants

### Data Management Committee:

Hao Deng, M.D., M.P.H.  
Tim Houle, Ph.D.

Responsibilities include: statistical design of trial, data verification.

### Data Adjudication Committee:

Oluwaseun Akeju, M.D., M.M.Sc.  
Shahzad Shaefi, M.D., MPH  
Brandon M Westover, M.D., Ph.D.

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.



1  
2  
3  
4  
5 Responsibilities include: regularly reviewing delirium assessments, contacting trial management  
6 committee, retraining researchers if necessary.  
7

8  
9 **Data and Safety Monitoring Committee:**

10 Wie Chao, M.D., Ph.D. - University of Maryland School of Medicine  
11 Jesse Ehrenfeld, M.D.,M.P.H. -Vanderbilt University Medical Center  
12 Michael Gropper, M.D., Ph.D. - University of California San Francisco  
13 Keith A. Jones, M.D. - The University of Alabama at Birmingham  
14

15 Responsibilities include: reviewing and evaluating the trial data to ensure participant safety, trial  
16 conduct, progress, and efficacy, and making recommendations regarding the continuation,  
17 modification, and termination of the trial.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

## Abstract

**Introduction:** Delirium, which is prevalent in post cardiac surgical patients, is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder. The pathophysiology of delirium remains poorly understood. However, basic science and clinical studies suggest that sleep disturbance may be a modifiable risk factor for the development of delirium. Dexmedetomidine is a  $\alpha_2$  adrenergic receptor agonist medication that patterns the activity patterns of various arousal nuclei similar to sleep. A single nighttime loading dose of dexmedetomidine promotes non-rapid eye movement sleep stages N2 and N3 sleep. This trial hypothesizes dexmedetomidine-induced sleep as pre-emptive therapy for postoperative delirium.

**Methods and Analysis:** The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is a 300-patient block-randomized, placebo-controlled, double-blinded, single-site, parallel-arm superiority trial. Patients over 60 years old, undergoing cardiac surgery with planned cardiopulmonary bypass, will be randomized to receive a sleep inducing dose of dexmedetomidine or placebo. The primary outcome is the incidence of delirium on postoperative day 1, assessed with the Confusion Assessment Method by staff blinded to the treatment assignment. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 300 patients receive the study intervention on post-operative day 0. Secondary outcomes will be evaluated by in-person assessments and medical record review for in-hospital end points, and by telephone interview for 30-day, 90-day, and 180-day end points. All trial outcomes will be evaluated using an intention-to-treat analysis plan. Hypothesis testing will be performed using a two-sided significance level (type I error) of  $\alpha=0.05$ . Sensitivity analyses using the actual treatment received will be performed and compared with the intention-to-treat analysis results.

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 Additional sensitivity analyses will assess the potential impact of missing data due to loss of  
4 follow-up.  
5  
6

7  
8 **Ethics and dissemination:** The Partners Human Research Committee approved the MINDDS  
9 trial. Recruitment began in March 2017. Dissemination plans include presentations at scientific  
10 conferences, scientific publications, and popular media.  
11  
12  
13

14 **Registration details:** NCT02856594.  
15  
16

### 17 **Strengths and limitations**

- 18 • The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-  
19 induced Sleep) will study whether biomimetic sleep will reduce the incidence of  
20 delirium.  
21  
22
- 23 • The trial intervention is based on a polysomnography study confirming that a  
24 nighttime loading dose of dexmedetomidine induces biomimetic sleep.  
25  
26
- 27 • The treatment protocol is straightforward and will allow the results to be generalized  
28 to patients across a range of care settings.  
29  
30
- 31 • Collection of patient-centered outcomes data, including measures of functional  
32 independence, at up to 180-days will provide insight into the relationship between the  
33 trial intervention and meaningful patient end points.  
34  
35
- 36 • Delirium is a fluctuating disorder that may occasionally be missed despite rigorous  
37 and validated assessment methods.  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

## Introduction

Delirium, which is prevalent in up to 48% of post cardiac surgical patients,<sup>1</sup> is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition that is not explained by a preexisting neurocognitive disorder.<sup>2</sup> It remains a leading cause of preventable morbidity and mortality in hospitalized elderly patients.<sup>3</sup> The morbidity associated with delirium is estimated to result in increased healthcare costs of approximately \$16,000-\$64,000 per patient annually. Increasing age and pre-existing cognitive impairment are key predisposing factors for delirium. Despite its impact, there are no definitive pharmacological preventative strategies for delirium. However, basic science and clinical studies suggest that sleep disturbances may be a modifiable risk factor for the development of delirium.

Sleep is a natural occurring state of decreased arousal that is crucial for normal cardiovascular, immune and cognitive function. Sleep deprivation, which is associated with increased pro-inflammatory cytokine levels including interleukin-6,<sup>4-6</sup> precedes the onset of delirium in patients.<sup>7,8</sup> A recent investigation linking brain activity of microglia, astrocytes, interleukin-6 and delirium in humans,<sup>9</sup> suggests a mechanistic link between sleep deprivation, brain inflammation, and delirium. Further, conditions associated with delirium are characterized by activation of the inflammatory cascade with acute release of inflammatory mediators.<sup>10-24</sup> Increasing age is a significant risk factor for the development of delirium. Notably, aging is associated with activated brain glia cell.<sup>3,25</sup> Following a systemic challenge such as critical illness, these activated glia have been suggested to facilitate an exaggerated neuroinflammatory state that predisposes to delirium.<sup>3,25-27</sup>

Sleep disturbance is a hallmark feature of the postoperative period,<sup>28-32</sup> and pharmacological induction of altered arousal states that are neurophysiologically indistinguishable from sleep, termed biomimetic sleep, may represent a preventative strategy for

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 the development of postoperative delirium. However, commonly administered sedative drugs,  
4 most of which modulate the  $\gamma$  amino butyric acid A (GABA<sub>A</sub>) receptor induce altered arousal  
5 states that are neurophysiologically distinct from sleep. This neurophysiological distinction from  
6 sleep (i.e. frontal beta oscillations, frontal alpha oscillations, burst suppression, isoelectricity)<sup>33-38</sup>  
7 may explain why current sedative medications that modulate GABA<sub>A</sub> receptors are not delirium  
8 sparing. Rather, neural circuit dysfunction in sensory, memory encoding, and cognitive  
9 processing circuits may in part explain why these medications are independent risk factors for  
10 the development of delirium.<sup>39</sup>  
11  
12  
13  
14  
15  
16  
17  
18  
19

20 Dexmedetomidine is a  $\alpha$ 2a adrenergic receptor agonist medication that patterns the  
21 activity patterns of various arousal nuclei similar to sleep.<sup>40-44</sup> Neurophysiologically, a continuous  
22 infusion of dexmedetomidine produces spindle and slow-delta oscillations.<sup>36,45</sup> This oscillatory  
23 dynamic shares features with non-rapid eye movement (REM) sleep stage N2 sleep.<sup>36,46,47</sup>  
24 Consistent with the hypothesis that the neurophysiological approximation of sleep may prevent  
25 delirium, the dexmedetomidine-infusion N2 sleep stage (with absent non-REM stages N1, N3  
26 and REM sleep) has been associated with a reduced incidence of delirium in critically ill  
27 patients.<sup>48-51</sup> Instead of a continuous drug infusion, we recently found that a single nighttime  
28 dose of dexmedetomidine preserves normal sleep cycling. This drug administration paradigm  
29 promotes non-REM stage N3 sleep. Notably, N3 sleep is associated with improved cognition  
30 and synaptic plasticity.<sup>52-60</sup>  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

44 A neurophysiologically principled approach to pharmacologically promote sleep may  
45 reduce significantly the incidence of delirium in hospitalized patients. The MINDDS (Minimizing  
46 ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial will evaluate  
47 dexmedetomidine-induced sleep as a pharmacological preventative strategy for delirium, and  
48 will characterize the impact of delirium prevention on patient-centered outcomes such as  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

1  
2  
3 functional recovery for up to 180-days. Risk factors and candidate mechanisms for the  
4 development of delirium such as intraoperative anesthetic management, perioperative  
5 electroencephalogram dynamics, and systemic inflammatory response will also be explored.  
6  
7  
8  
9

## 10 **Trial objectives**

11  
12 Our primary hypothesis is that dexmedetomidine-induced sleep will result in a reduced  
13 incidence of delirium. Our intervention and control groups will be comprised of extubated  
14 cardiac surgical intensive care unit (CSICU) patients, because their relative homogeneity in  
15 terms of surgical procedures (i.e. cardiac surgery performed on cardiopulmonary bypass),  
16 anesthetic management, and systemic inflammatory response represents a unique opportunity  
17 to study the mechanisms underlying delirium, while limiting confounding factors that may  
18 otherwise be encountered in heterogeneous patients  
19  
20  
21  
22  
23  
24  
25  
26

## 27 **Methods and analysis**

### 28 **Trial design**

29  
30 We will enroll 300 patients over a period of three years into a randomized, controlled,  
31 double-blinded, single-site, parallel-arm superiority trial. Our primary outcome is the incidence of  
32 delirium on postoperative day 1 upon administration of the study intervention. To ensure that the  
33 study is appropriately powered for the primary outcome measure, patients will be recruited and  
34 randomized into the study until 300 patients receive the study intervention on post-operative day  
35 0. Trial end points will be assessed via in-person interview (during hospitalization), medical  
36 record review, and telephone interview (after hospital discharge). The primary and secondary  
37 outcomes of delirium will be assessed via in-person interviews, which will be performed in the  
38 morning and afternoon with approximately 6 hours between interviews. All outcomes, including  
39 those obtained post discharge, will be assessed in a blinded fashion.  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51

### 52 **Eligibility criteria**

53  
54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

**Inclusion criteria**

1. Age  $\geq$  60
2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for  $\geq$  24 hours
3. Scheduled same day surgical admission

**Exclusion criteria**

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score  $>$  5
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit
9. Surgical procedure requiring total circulatory arrest

**Objective Drop Criteria**

1. Surgical procedure scheduled as second case of the day, and/or to be commenced after 12pm
2. Scheduled for a second surgical procedure during hospital stay
3. Postoperative intubation  $>$  12 hours

**Baseline assessment**

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 Patients will undergo a pre-randomization assessment that includes a brief medical  
4 record review, and evaluation the following:

- 5  
6  
7 1. Baseline cognitive function using the telephone Montreal Cognitive Assessment
- 8  
9  
10 2. Presence of delirium at the time of interview, as measured by the 3 min assessment for  
11  
12 Confusion Assessment Method-defined delirium (3D-CAM)
- 13  
14 3. Physical function with the PROMIS SF v1.2 -Physical function 8b
- 15  
16 4. General health with the PROMIS SF v1.1- Global
- 17  
18 5. Pain with the PROMIS SF v1.0- Pain Interference 8a
- 19  
20 6. Applied cognition with the PROMIS v1.0- Applied Cognition Abilities SF 8a
- 21  
22 7. Baseline sleep quality with the PROMIS-4A
- 23  
24  
25  
26

## 27 **Intervention**

28  
29 We will randomly allocate patients to receive placebo or dexmedetomidine nightly during  
30 their CSICU stay. All clinical care during preoperative, intraoperative and postoperative periods  
31 will follow normal standard of care. However, trial patients admitted to the CSICU and extubated  
32 at least 30 minutes prior to 8.30 PM would receive a sleep induction dose of dexmedetomidine  
33 (1mcg/kg over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients  
34 admitted to the CSICU and extubated after 8.30 PM, but before 2 AM, would receive a sleep  
35 induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the  
36 rest of the CSICU stay the sleep induction time will be targeted for 9 PM. Trial patients who are  
37 admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following  
38 day, assuming they are extubated within 12 hours of admission to the CSICU. The maximum  
39 dexmedetomidine dose that will be administered is 80 mcg. Clinicians will be asked to refrain  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59



1  
2  
3 from routinely administering dexmedetomidine to patients in the operating room and in the  
4 CSICU. Otherwise, all other care decisions will be at the discretion of the clinical care team.  
5  
6

## 7 **Outcomes**

### 8 **Primary outcome**

9  
10 The primary outcome measure for this trial is the incidence delirium in the CSICU on  
11 postoperative day 1. Delirium assessments will be conducted twice daily (AM and PM with at  
12 least 6 hours between tests) beginning on postoperative day 1 using the Long Confusion  
13 Assessment Method (CAM).<sup>61,62</sup> Trial staff blinded to treatment assignments will perform the  
14 delirium assessments. Delirium assessments for patients who are reintubated for clinical care or  
15 for further surgical management will be considered missing data.  
16  
17  
18  
19  
20  
21  
22

### 23 **Secondary outcomes (in-hospital)**

24  
25 Blinded trial staff will collect secondary outcomes during hospital admission. These  
26 outcomes include:  
27

- 28 1. ICU and hospital delirium/coma-free days assessed twice daily through postoperative  
29 day 3, or up until postoperative day 7 or discharge for patients who are delirious beyond  
30 postoperative day 5  
31
- 32 2. Severity of delirium scored using the CAM delirium severity scoring long form  
33
- 34 3. Date of hospital discharge and length of hospital stay assessed by chart review  
35
- 36 4. Inpatient mortality and major inpatient morbidity assessed by chart review  
37
- 38 5. Peri-operative EEG dynamics of delirium  
39  
40  
41  
42  
43

### 44 **Secondary outcomes (post-discharge)**

45  
46 Blinded trial staff will collect secondary outcomes via telephone interviews and/or online  
47 questionnaires at 30-days, 90-days, and 180-days post procedure. These outcomes include:  
48

- 49 1. Cognitive function using the telephone Montreal Cognitive Assessment  
50
- 51 2. Physical function with the PROMIS SF v1.2 - Physical Function 8b  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

3. General health with the PROMIS SF v1.1 - Global
4. Pain with the PROMIS SF v1.0- Pain Interference 8a
5. Applied cognition with the PROMIS v1.0 - Applied Cognition Abilities SF 8a
6. Sleep quality with the PROMIS v1.0 - Sleep Disturbance 4A
7. Mortality

### Sample size planning

The primary objective of this trial is to detect a difference in the incidence of delirium between the dexmedetomidine-induced sleep and normal care groups. Assuming a delirium event rate of 48%, a type I error of 0.05, and power of 0.80, an n = 150 patients per group will enable us to detect an absolute difference 15% (i.e., 48% versus 33%). With respect to decreased morbidity and healthcare costs, this change represents a clinically meaningful difference. Therefore, we will recruit up to 150 patients per group.

### Recruitment

This study will be performed at the Massachusetts General Hospital in Boston, MA. Subjects will be recruited through the cardiac surgery preoperative clinic and all enrolled patients will provide written informed consent. Informed consent for this protocol will follow a two-part process. First, a verbal consent will be obtained at the pre-operative visit prior to administering pre-operative baseline questionnaires. During this visit, the trial protocol will be explained to potential participants. In addition, a flyer detailing an overview of the trial protocol, as well as a copy of the formal consent form, will be given to potential trial participants to take home. A study physician will obtain final, written consent on the day of surgery (typically within 14 days of the pre-operative visit). After written consent is obtained, the trial team will allocate a trial identification number to the subject based on the trial stratification schema. A clinical trial pharmacist will perform central allocation into study arms according to the randomization key

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 that is associated with each trial identification number.  
4

### 5 **Allocation**

6 Eligible patients who provide written informed consent will be randomized to receive  
7 either dexmedetomidine or placebo with a 1:1 allocation as per a computer generated  
8 randomization schedule generated by an independent statistician, and stratified by cardiac  
9 surgery type (i.e. valvular repair versus non-valvular repair) using permuted blocks of random  
10 sizes. The block sizes will not be disclosed until the primary endpoint is analyzed to ensure  
11 concealment. Allocation concealment is further ensured by the fact that dexmedetomidine and  
12 placebo cannot be distinguished on the basis of appearance. The randomization key that is  
13 associated with each participant trial identification number will remain with the clinical trial  
14 pharmacist (AD) for the duration of the study. Thus, the clinical trial pharmacist will conduct  
15 randomization throughout the study in order to keep the data management and the statistician  
16 blind. All trial medications will be labeled as “dexmedetomidine or placebo,” to preserve the  
17 integrity of randomization assignments. Thus, randomization into any study arm will be  
18 conducted without any influence of the study investigators, biostatisticians, and outcome  
19 assessors. The CSICU nurse taking care of the patient will administer the trial medication. If  
20 other medications are indicated for the treatment of delirium, the treating physician will prescribe  
21 this as part of standard clinical care.  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39

### 40 **Blinding**

41 Assessors who are blind to treatment allocation will conduct all primary and secondary outcome  
42 assessments. To maintain the overall quality and legitimacy of the clinical trial, code breaks will  
43 occur only in exceptional circumstances when knowledge of the actual treatment is deemed  
44 essential by the treating physicians for further management of the patient. The treating  
45 physician will be directed to the clinical trial pharmacist to obtain the actual treatment code. The  
46 study investigators will maintain blindness and the treatment allocation. Additionally, the treating  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

1  
2  
3 physician will be directed to abstain from written or verbal disclosure of the code. The principal  
4  
5 investigator (PI) will report all code breaks to the DSMB.  
6

### 7 **Criteria for patient discontinuation**

8  
9 Patients may be discontinued from trial treatment and assessments for several reasons.  
10  
11 These include: voluntary discontinuation by the patient, safety reasons (i.e. active hemorrhage)  
12  
13 as judged by the clinical and/or trial physicians, failure to maintain study eligibility during the  
14  
15 hospital stay or non-compliance with the protocol as judged by the trial physician.  
16

### 17 **Data analysis**

18  
19 All trial outcomes will be evaluated using a modified intention-to-treat analysis plan.  
20  
21 Hypothesis tests will be performed using a two-sided significance level (type I error) of  $\alpha=0.05$ .  
22  
23 Sensitivity analyses using the actual treatment received will also be performed and compared  
24  
25 with the intention-to-treat analysis results. Additional sensitivity analyses will be performed to  
26  
27 assess the potential impact of missing data due to follow-up losses. The primary outcome will  
28  
29 be evaluated using logistic regression examining the presence or absence of delirium  
30  
31 conditional on randomized group assignment. Any randomization imbalances, or other potential  
32  
33 treatment effect modifiers will be further examined as covariates in sensitivity analyses.  
34  
35 Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will  
36  
37 use Pearson  $\chi^2$  tests to compare categorical variables between the 2 trial groups and  
38  
39 independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event  
40  
41 analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal  
42  
43 care on mortality, and CSICU and hospital lengths of stay. Kaplan-Meier survival curves will be  
44  
45 used for graphical presentation of these time-to-event analyses, and log-rank statistics will be  
46  
47 used to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients  
48  
49 will be censored at the time of last contact alive. Censoring for CSICU or hospital discharge  
50  
51 readiness analyses will occur at time of death or trial withdrawal. Because missing data rarely  
52  
53

54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56  
57 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
58  
59 published or disclosed without prior written approval.  
60

1  
2  
3 occur entirely at random, we will assess the associations between patient characteristics with  
4 respect to missing data. If patients with at least one missing outcome value are different from  
5 those with complete outcomes data, we will use multiple imputation to assign values to missing  
6 data risk factors and outcomes in regression modeling.  
7  
8  
9  
10

### 11 **Heterogeneity of treatment effects**

12  
13  
14 Subgroup comparisons will be conducted for heterogeneity of treatment–covariate  
15 interactions if the sample sizes and numbers of events within these subgroups are sufficient for  
16 analysis. If there is a treatment difference together with evidence of heterogeneity, relevant  
17 covariates and interaction terms will be added to the relevant regression models for formal  
18 significance testing. For the primary outcome, we plan for analyses of treatment effects within  
19 pre-specified subgroups potentially defined by:  
20  
21  
22  
23  
24  
25

- 26 1. Surgery type
  - 27 2. Length of cardiopulmonary bypass
  - 28 3. Presence of significant cardiac dysfunction (ejection fraction less than 35%)
  - 29 4. Sedative administration in the ICU
  - 30 5. Opioid administration in the ICU
  - 31 6. Pain scores
  - 32 7. Baseline cognitive status
  - 33 8. Organ failure
  - 34 9. Postoperative cerebrovascular disease
  - 35 10. APACHE/EUROscore
- 36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

### 48 **Interim analyses**

49  
50 Interim efficacy data will be provided to the Data Safety Monitoring Board (DSMB) during  
51 yearly meetings to permit benefit-to-risk assessments. An independent statistician that is  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

1  
2  
3 unblinded to the treatment allocation will perform the interim-analysis. The statistician will report  
4 to the DSMB in a closed session. Thus, the DSMB will have unblinded access to all data to  
5 inform recommendations on study continuation. If at any time during the course of the study the  
6 DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the  
7 discretion and responsibility to recommend that the study be terminated.  
8  
9  
10  
11  
12

### 13 **Data management**

14  
15  
16 All data collected for the MINDDS trial will be entered into the Massachusetts General  
17 Hospital Research Electronic Data Capture (REDCap) application.<sup>63</sup> Data entered into the  
18 database will be retrievable for viewing through the data entry applications. Data integrity will be  
19 enforced through referential data rules, valid values, range checks, and consistency checks  
20 against data already stored in the database. Programs designed to detect missing data or  
21 specific errors in the data will be implemented to detect additional errors. These errors will be  
22 summarized along with detailed descriptions for each specific problem in monthly Data Query  
23 Reports, which will be sent to the PI. The PI will respond by checking the original forms for  
24 inconsistency, checking other sources to determine the correction, modifying the original forms  
25 as necessary, and entering a response to the query. Data access will be restricted via password  
26 protection to only those individuals who are authorized to work on the trial. Specific privilege  
27 assignments within the database will also be employed to limit the types of data that authorized  
28 users may access to the minimum required by their role in the trial. Electronic audit trails will be  
29 used to capture and record changes to database contents automatically. Original study forms  
30 will also be kept in files. Participant files will be stored in numerical order in a secure and  
31 accessible place and manner. These files will be maintained in storage for a period of at least 5  
32 years after study completion. Members of the adjudication committee will request a subset of  
33 these study forms later for quality control.  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

## Site training

Trial team members have undergone a rigorous CAM training program led by a neuropsychologist and member of the team that created the Long-CAM.<sup>62</sup> The CAM is the most widely used delirium assessment tool in the research setting, with a high sensitivity and specificity when compared with formal psychiatric diagnosis.<sup>61,62</sup> The 3D-CAM is a three-minute assessment tool for delirium, which has good agreement with the CAM.<sup>64</sup> Those who attended this initial training will oversee the training of other team members. All trainees must demonstrate competence at conducting the structured interviews and in correctly scoring subjects. Trainees must first conduct at least two satisfactory CAM assessments in subjects not enrolled in the MINDDS trial in the presence of a trained team member. To establish competency in scoring the CAM, trainees will observe CAM interviews conducted by trained team members and will score the CAM independently. The trainee must agree with the trainer on the presence or absence of all cognitive features assessed by the CAM on a minimum of six interviews. After meeting the stipulations of training, the newly trained team member will conduct their first interview of a patient enrolled into the MINDDS trial in the presence of a previously trained team member. Independent of the training process, all MINDDS team members who are participating in CAM assessments must view and rate videos of CAM interviews of actors depicting delirious and non-delirious patients.

## Data and safety monitoring

All unexpected adverse events that are related to the trial treatment will be recorded in the trial database and reported as required to the Partners Healthcare IRB. A data and safety monitoring board (DSMB) will also oversee the MINDDS trial. The DSMB will provide independent oversight of the MINDDS, and will review general conduct of the trial and trial data for participant safety. The DSMB is comprised of independent, multidisciplinary experts who will

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.



1  
2  
3 make recommendations regarding the continuation, modification, or termination of the trial. The  
4  
5 members will have the requisite expertise to examine accumulating data, to protect the integrity  
6  
7 of the clinical experiments to which the patients have consented to participate, and to assure the  
8  
9 regulatory bodies, the public and the National Institutes of Health that conflicts of interest do not  
10  
11 compromise either patient safety or trial integrity. The DSMB will convene before trial initiation  
12  
13 and annually to review safety events. Recommendations from the DSMB for protocol  
14  
15 modifications or revisions will be communicated through a representative of the National  
16  
17 Institutes on Aging to the PI.  
18  
19

20 The study operations committee will determine relatedness of an event to the study drug  
21  
22 based on a temporal relationship to the study drug administration, whether the event is  
23  
24 unexpected given the clinical course, previous medical conditions, and concomitant  
25  
26 medications. Adverse events will also be communicated to members of the study steering  
27  
28 committee for additional review. Expedited review will occur for all events meeting the FDA  
29  
30 definition of SAEs – i.e., any fatal event, immediately life-threatening event, permanently or  
31  
32 substantially disabling event, or event requiring or prolonging inpatient hospitalization. This also  
33  
34 includes any event that a study investigator or the DSMB judges to impose a significant hazard,  
35  
36 contraindication, side effect, or precaution. For purposes of this study, all SAEs will require  
37  
38 reporting to the DSMB, regardless of their relatedness to the study drug. All relevant information  
39  
40 will be reported to the DSMB for each SAE, including information about the event and its  
41  
42 outcome, dosing history of all study drugs, concomitant medications, the subject's medical  
43  
44 history and current conditions, and all relevant laboratory data. Notification by e-mail of all  
45  
46 related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE.  
47  
48 Information will be reviewed and a determination made of whether there was any possible  
49  
50 relevance to the study drug. Additional reporting to the IRB will be done within 24 hours of the  
51  
52 SAE. All patients that experience a SAE will be censored from the study at SAE occurrence.  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56  
57 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
58  
59 published or disclosed without prior written approval.  
60



## Data Monitoring and Quality Assurance

Reflective of the state of the art in clinical trials, the MINNDS trial will employ a web-based portal for data quality and completeness. The portal will display in real time the following variables for all patients: sex, race, adverse events, study related data etc.

## Trial risks

The risk of a breach of confidentiality is small and all possible efforts have been taken to ensure the security of trial data and minimize the risks of accidental disclosure of identifiable data elements. The risks associated with dexmedetomidine are related to drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. However, cardiovascular parameters are continuously monitored in the CSICU, ensuring that appropriate medical intervention can be instituted in a timely fashion for clinically significant hypotensive or bradycardic episodes. Thus, the risk of clinically significant hypotension or bradycardia in our patient study population is small.

## Ethics and dissemination

The trial has been approved by the Partners Health Care IRB. The trial steering committee will be responsible for all major decisions regarding changes to the protocol. The committee will communicate these changes to the IRB and the DSMB. Electronic data and demographic information will be accessed only as necessary for completion of trial follow-up tasks. The PI has will have access to all data. The primary papers emanating from MINDDDS will present primary and secondary outcome. Secondary analyses will also be conducted to construct predictive models for delirium occurrence and resource utilization. Mechanistic manuscripts on the pathophysiology, which will be based on biomarkers elicited from MINNDS study participants (i.e. perioperative electroencephalogram, serum, brain imaging) will also be published. Dissemination plans include presentations at local, national and international scientific conferences. Every effort will be made to publish results of the MINDDDS trial in a peer-

CONFIDENTIAL: This document is the intellectual property the MINDDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 reviewed journal. Dissemination of results to trial participants and their family members will be  
4 available upon request. Updates and results of the trial will be available to the public at  
5 clinicaltrials.gov.  
6  
7  
8

### 9 **Conclusion**

10  
11 The MINDDS trial will evaluate a new preemptive therapeutic sleep strategy for the  
12 prevention of delirium, and may enable new insights into the pathophysiology of delirium.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

## References

1. Rudolph JL, Inouye SK, Jones RN, Yang FM, Fong TG, Levkoff SE, Marcantonio ER: Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010; 58: 643-9
2. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force.: Diagnostic and statistical manual of mental disorders : DSM-5, 5th edition. Washington, D.C., American Psychiatric Association, 2013
3. Maldonado JR: Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry* 2013; 21: 1190-222
4. Shearer WT, Reuben JM, Mullington JM, Price NJ, Lee BN, Smith EO, Szuba MP, Van Dongen HP, Dinges DF: Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* 2001; 107: 165-70
5. Haack M, Sanchez E, Mullington JM: Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* 2007; 30: 1145-52
6. Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP: Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab* 2004; 89: 2119-26
7. Johns MW, Large AA, Masterton JP, Dudley HA: Sleep and delirium after open heart surgery. *Br J Surg* 1974; 61: 377-81
8. Mundigler G, Delle-Karth G, Koreny M, Zehetgruber M, Steindl-Munda P, Marktl W, Ferti L, Siostrzonek P: Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med* 2002; 30: 536-40
9. Munster BC, Aronica E, Zwinderman AH, Eikelenboom P, Cunningham C, Rooij SE: Neuroinflammation in delirium: a postmortem case-control study. *Rejuvenation Res* 2011; 14: 615-22
10. Siami S, Annane D, Sharshar T: The encephalopathy in sepsis. *Crit Care Clin* 2008; 24: 67-82, viii
11. O'Keefe ST, Ni Chonchubhair A: Postoperative delirium in the elderly. *Br J Anaesth* 1994; 73: 673-87
12. Lenz A, Franklin GA, Cheadle WG: Systemic inflammation after trauma. *Injury* 2007; 38: 1336-45
13. Shimaoka M, Park EJ: Advances in understanding sepsis. *Eur J Anaesthesiol Suppl* 2008; 42: 146-53
14. Weichhart T, Haidinger M, Horl WH, Saemann MD: Current concepts of molecular defence mechanisms operative during urinary tract infection. *Eur J Clin Invest* 2008; 38 Suppl 2: 29-38
15. Bjornsson GL, Thorsteinsson L, Gudmundsson KO, Jonsson H, Jr., Gudmundsson S, Gudbjornsson B: Inflammatory cytokines in relation to adrenal response following total hip replacement. *Scand J Immunol* 2007; 65: 99-105
16. Kragstjerg P, Holmberg H, Vikerfors T: Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. *Eur J Surg* 1995; 161: 17-22
17. Keck M, Herndon DH, Kamolz LP, Frey M, Jeschke MG: Pathophysiology of burns. *Wien Med Wochenschr* 2009; 159: 327-36
18. Marx N, Neumann FJ, Ott I, Gawaz M, Koch W, Pinkau T, Schomig A: Induction of cytokine expression in leukocytes in acute myocardial infarction. *J Am Coll Cardiol* 1997; 30: 165-70

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

19. Asimakopoulos G: Mechanisms of the systemic inflammatory response. *Perfusion* 1999; 14: 269-77
20. Sun Y, Tawara I, Toubai T, Reddy P: Pathophysiology of acute graft-versus-host disease: recent advances. *Transl Res* 2007; 150: 197-214
21. Stinghen AE, Goncalves SM, Martinez EG, Nakao LS, Riella MC, Aita CA, Pecoits-Filho R: Increased plasma and endothelial cell expression of chemokines and adhesion molecules in chronic kidney disease. *Nephron Clin Pract* 2009; 111: c117-26
22. Shawcross DL, Shabbir SS, Taylor NJ, Hughes RD: Ammonia and the neutrophil in the pathogenesis of hepatic encephalopathy in cirrhosis. *Hepatology* 2010; 51: 1062-9
23. van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE: Time-course of cytokines during delirium in elderly patients with hip fractures. *J Am Geriatr Soc* 2008; 56: 1704-9
24. Culley DJ, Snayd M, Baxter MG, Xie Z, Lee IH, Rudolph J, Inouye SK, Marcantonio ER, Crosby G: Systemic inflammation impairs attention and cognitive flexibility but not associative learning in aged rats: possible implications for delirium. *Front Aging Neurosci* 2014; 6: 107
25. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB: The neuroinflammatory hypothesis of delirium. *Acta Neuropathol* 2010; 119: 737-54
26. Norden DM, Godbout JP: Review: microglia of the aged brain: primed to be activated and resistant to regulation. *Neuropathol Appl Neurobiol* 2013; 39: 19-34
27. Cunningham C: Systemic inflammation and delirium: important co-factors in the progression of dementia. *Biochem Soc Trans* 2011; 39: 945-53
28. Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J: Postoperative sleep disturbances: mechanisms and clinical implications. *Br J Anaesth* 1996; 76: 552-9
29. Aurell J, Elmqvist D: Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *Br Med J (Clin Res Ed)* 1985; 290: 1029-32
30. Ellis BW, Dudley HA: Some aspects of sleep research in surgical stress. *J Psychosom Res* 1976; 20: 303-8
31. Kavey NB, Ahshuler KZ: Sleep in herniorrhaphy patients. *Am J Surg* 1979; 138: 683-7
32. Lehmkuhl P, Prass D, Pichlmayr I: General anesthesia and postnarcotic sleep disorders. *Neuropsychobiology* 1987; 18: 37-42
33. van Lier H, Drinkenburg WH, van Eeten YJ, Coenen AM: Effects of diazepam and zolpidem on EEG beta frequencies are behavior-specific in rats. *Neuropharmacology* 2004; 47: 163-74
34. Feinberg I, Maloney T, Campbell IG: Effects of hypnotics on the sleep EEG of healthy young adults: new data and psychopharmacologic implications. *J Psychiatr Res* 2000; 34: 423-38
35. Patat A, Trocherie S, Thebault JJ, Rosenzweig P, Dubruc C, Bianchetti G, Court LA, Morselli PL: EEG profile of intravenous zolpidem in healthy volunteers. *Psychopharmacology (Berl)* 1994; 114: 138-46
36. Akeju O, Pavone KJ, Westover MB, Vazquez R, Prerau MJ, Harrell PG, Hartnack KE, Rhee J, Sampson AL, Habeeb K, Gao L, Pierce ET, Walsh JL, Brown EN, Purdon PL: A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. *Anesthesiology* 2014; 121: 978-89
37. Akeju O, Westover MB, Pavone KJ, Sampson AL, Hartnack KE, Brown EN, Purdon PL: Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. *Anesthesiology* 2014; 121: 990-8
38. Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, Ching S, Kopell NJ, Tavares-Stoeckel C, Habeeb K,

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

- 1  
2  
3 Merhar R, Brown EN: Electroencephalogram signatures of loss and recovery of consciousness  
4 from propofol. *Proc Natl Acad Sci U S A* 2013; 110: E1142-51
- 5 39. American Geriatrics Society Beers Criteria Update Expert P: American Geriatrics Society  
6 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr*  
7 *Soc* 2012; 60: 616-31
- 8 40. Correa-Sales C, Rabin BC, Maze M: A hypnotic response to dexmedetomidine, an alpha  
9 2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology* 1992; 76: 948-52
- 10 41. Lu J, Nelson LE, Franks N, Maze M, Chamberlin NL, Saper CB: Role of endogenous  
11 sleep-wake and analgesic systems in anesthesia. *J Comp Neurol* 2008; 508: 648-62
- 12 42. Mizobe T, Maghsoudi K, Sitwala K, Tianzhi G, Ou J, Maze M: Antisense technology  
13 reveals the alpha2A adrenoceptor to be the subtype mediating the hypnotic response to the  
14 highly selective agonist, dexmedetomidine, in the locus coeruleus of the rat. *J Clin Invest* 1996;  
15 98: 1076-80
- 16 43. Nacif-Coelho C, Correa-Sales C, Chang LL, Maze M: Perturbation of ion channel  
17 conductance alters the hypnotic response to the alpha 2-adrenergic agonist dexmedetomidine  
18 in the locus coeruleus of the rat. *Anesthesiology* 1994; 81: 1527-34
- 19 44. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M: The alpha2-adrenoceptor  
20 agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its  
21 sedative effects. *Anesthesiology* 2003; 98: 428-36
- 22 45. Huupponen E, Maksimow A, Lapinlampi P, Sarkela M, Saastamoinen A, Snapir A,  
23 Scheinin H, Scheinin M, Merilainen P, Himanen SL, Jaaskelainen S: Electroencephalogram  
24 spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol*  
25 *Scand* 2008; 52: 289-94
- 26 46. Alexopoulou C, Kondili E, Diamantaki E, Psarologakis C, Kokkini S, Bolaki M,  
27 Georgopoulos D: Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot  
28 study. *Anesthesiology* 2014; 121: 801-7
- 29 47. Oto J, Yamamoto K, Koike S, Onodera M, Imanaka H, Nishimura M: Sleep quality of  
30 mechanically ventilated patients sedated with dexmedetomidine. *Intensive Care Med* 2012; 38:  
31 1982-9
- 32 48. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P,  
33 Margolis BD, Byrne DW, Ely EW, Rocha MG, Group SS: Dexmedetomidine vs midazolam for  
34 sedation of critically ill patients: a randomized trial. *JAMA* 2009; 301: 489-99
- 35 49. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK,  
36 Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW: Effect of  
37 sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically  
38 ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; 298: 2644-53
- 39 50. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, Davies A,  
40 Delaney A, Ghosh A, van Haren F, Harley N, Knight D, McGuinness S, Mulder J, O'Donoghue S,  
41 Simpson N, Young P, Dah LIAI, the A, New Zealand Intensive Care Society Clinical Trials G:  
42 Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With  
43 Agitated Delirium: A Randomized Clinical Trial. *JAMA* 2016; 316: 773-4
- 44 51. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA:  
45 Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery.  
46 *Psychosomatics* 2009; 50: 206-17
- 47 52. Wafford KA, Ebert B: Emerging anti-insomnia drugs: tackling sleeplessness and the  
48 quality of wake time. *Nat Rev Drug Discov* 2008; 7: 530-40
- 49 53. Huber R, Ghilardi MF, Massimini M, Tononi G: Local sleep and learning. *Nature* 2004;  
50 430: 78-81

51  
52  
53  
54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.



- 1  
2  
3 54. Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, Tononi G: Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat Neurosci* 2006; 9: 1169-76
- 4  
5  
6 55. Huber R, Tononi G, Cirelli C: Exploratory behavior, cortical BDNF expression, and sleep homeostasis. *Sleep* 2007; 30: 129-39
- 7  
8 56. Rasch B, Buchel C, Gais S, Born J: Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science* 2007; 315: 1426-9
- 9  
10 57. Backhaus J, Junghanns K, Born J, Hohaus K, Faasch F, Hohagen F: Impaired declarative memory consolidation during sleep in patients with primary insomnia: Influence of sleep architecture and nocturnal cortisol release. *Biol Psychiatry* 2006; 60: 1324-30
- 11  
12 58. Molle M, Marshall L, Gais S, Born J: Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. *Proc Natl Acad Sci U S A* 2004; 101: 13963-8
- 13  
14  
15 59. Prehn-Kristensen A, Munz M, Goder R, Wilhelm I, Korr K, Vahl W, Wiesner CD, Baving L: Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. *Brain Stimul* 2014; 7: 793-9
- 16  
17 60. Marshall L, Molle M, Hallschmid M, Born J: Transcranial direct current stimulation during sleep improves declarative memory. *J Neurosci* 2004; 24: 9985-92
- 18  
19 61. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI: Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990; 113: 941-8
- 20  
21 62. Ramaswamy R, Dix EF, Drew JE, Diamond JJ, Inouye SK, Roehl BJ: Beyond grand rounds: a comprehensive and sequential intervention to improve identification of delirium. *Gerontologist* 2011; 51: 122-31
- 22  
23 63. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377-81
- 24  
25 64. Marcantonio ER, Ngo LH, O'Connor M, Jones RN, Crane PK, Metzger ED, Inouye SK: 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med* 2014; 161: 554-61
- 26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

### Authorship Eligibility and Contributorship

Authorship for this trial will be given to key personnel involved in trial design, recruitment, data collection, and data analysis. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript. KTS, JQ, GC, HD, EYH, LEH, TTH, RI, KJP, and OA were responsible for conceptualizing trial design. JQ managed patient safety protocol. EYH, RI, and LH were responsible for recruitment, enrolment, and data collection. KTS, JQ, FB, ENB, GC, DAD, HD, AD, EYH, LEH, TTH, RI, ML, KJP, SS, GT, MBW, and OA have critically revised the MINDDS protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the MINDDS trial.

For peer review only

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

# Minimizing ICU neurological dysfunction with dexmedetomidine-induced sleep (MINDDS): A randomized placebo-controlled trial

**Principal Investigator:** Oluwaseun Johnson-Akeju, M.D., M.M.Sc

## 1. BACKGROUND AND SIGNIFICANCE

Delirium is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder.<sup>1</sup> It is associated with increased mortality, prolonged hospitalization, prolonged institutionalization, and long-term cognitive deficits.<sup>2-7</sup> Patients with pre-existing dementia, such as Alzheimer's disease, are especially vulnerable to developing delirium.<sup>8</sup> The total healthcare cost attributable to delirium is estimated between \$143 and \$152 billion annually.<sup>9</sup> In the United States, delirium occurs in approximately 80% of critically ill patients admitted to medical/surgical intensive care units (ICU),<sup>10</sup> and 43% of patients admitted to cardiac surgical (CS) ICU.<sup>11</sup> Most patients diagnosed with delirium also present with multiple comorbidities (sepsis, multi-organ failure) that significantly confound our understanding of this disease.<sup>2</sup> Thus, to date, no pharmacological intervention to treat delirium has been identified.<sup>2</sup> The aging process has been identified as a risk factor for developing delirium.

Normal aging is associated with a morphological shift of glia (microglia, astrocytes) to an activated state. Following a systemic challenge such as critical illness, these activated glia aid a neuroinflammatory state that contributes to delirium. The aforementioned neuroinflammatory state is exacerbated by sleep disturbances.<sup>15-17</sup> Thus, sleep deprivation may be a modifiable risk factor for the development of delirium. Presently, pharmacological treatment with no current medication (benzodiazepines, antipsychotics) induces natural sleep or reliably reduces the incidence of delirium. **We have found that pharmacological induction of rapid eye movement sleep (REM) and non-REM I-III sleep states using dexmedetomidine, can now be safely achieved in humans.** Our overall objective is to evaluate the efficacy of dexmedetomidine-induced sleep in preventing delirium, investigate cellular and molecular mechanisms underlying delirium, and investigate whether recently described intraoperative electroencephalogram (EEG) signatures of the aging brain are associated with developing delirium.<sup>18</sup> Our central hypothesis is that nightly biomimetic sleep in elderly patients admitted to the CSICU for > 24hrs will reduce the incidence of ICU delirium.

Our intervention and control groups will be comprised of extubated CSICU patients, because their homogeneity in terms of surgical procedures, anesthetic management, and systemic inflammatory response represents a unique opportunity to study the mechanisms underlying delirium, while limiting confounding factors that may otherwise be encountered in heterogeneous patients found in the medical/surgical ICU. We will perform assessments of cognition (peri-operative), obtain EEG recordings (intra-operative, ICU) and blood samples (peri-operative).

At the conclusion of these studies, we will have expanded our knowledge of the pathophysiology of delirium, evaluated a new preemptive therapeutic strategy for delirium, suggest neurophysiologically based monitoring strategies to reduce significantly the amount of anesthetic administered to elderly patients – and possibly delirium – while being certain the patient is sufficiently unconscious for surgery (individualized anesthesia care), and enable continued investigation into the pathophysiology of this clinically important disorder.

## 2. SPECIFIC AIMS

We will pursue three aims. In the first aim, we will investigate the benefits of preemptive biomimetic sleep for reducing the risk of developing delirium in a randomized controlled trial; in the second aim, we will investigate the mechanisms of delirium using serum metabolic profiling; and in the third aim, we will investigate predictors of delirium from perioperative EEG recordings. **Table 1** shows a proposed timeline.

Hypothesis	Short Name	Year 1	Year 2	Year 3	Year 4	Year 5
1.1	Nightly preemptive biomimetic sleep will reduce the incidence of delirium	..	..	..		
2.1	Serum metabolic profiling will be sensitive to detect neurodegeneration of preclinical delirium			..	..	
3.1	Absence of anesthesia-induced frontal alpha oscillations will be associated with delirium			..	..	..



1	3.2	Burst-suppression/anesthesia overdose will be associated with delirium			..	..	..
2							
3							
4							

The specific aims of this study are:

**AIM 1: Investigate the benefits of preemptive biomimetic sleep for reducing the risk of delirium in a Randomized Controlled Trial.**

Hypothesis 1.1. Compared to standard treatments (benzodiazepines, antipsychotics), nightly preemptive biomimetic sleep will reduce the incidence of ICU delirium.

**AIM 2: Investigate mechanisms of delirium using serum metabolic profiling.**

Hypothesis 2.1. Unbiased serum metabolic profiling will be sensitive to detect early signatures of neurodegeneration that predisposes to the development of delirium.

**AIM 3: Investigate predictors of delirium from perioperative EEG recordings.**

Hypothesis 3.1. The relative absence of anesthesia-induced frontal alpha oscillations (a putative marker of brain vulnerability) is associated with delirium.

Hypothesis 3.2. Burst-suppression induced by the age-adjusted maintenance anesthetic (a putative marker of anesthetic overdose and brain vulnerability) is associated with the severity of delirium.

### 3. STUDY PROCEDURES

**Subject Selection:** We will enroll 300 patients over a period of three years into a randomized, controlled, double-blinded, single-site, parallel-arm superiority trial. Our primary outcome is the incidence of delirium on postoperative day 1 upon administration of the study intervention. Thus, in order to ensure that we are adequately powered, patients will be censored from the study if they do not receive dexmedetomidine or placebo on postoperative day 0. The cardiac surgical case volume at Massachusetts General Hospital (MGH) will enable us to meet our recruitment goals within our projected timeline. Cardiac surgeons, cardiac intensivists, and anesthesiologists at MGH will identify all potential study participants. This initial care provider-patient contact will ensure that eligible patients are comfortable with all study procedures. Once the potential participant confirms that he/she is comfortable with all study procedures, a copy of the consent form will be made available. Informed consent for this protocol will follow a two part process. First, a verbal consent will be obtained at the Department of Anesthesia, Critical Care and Pain Medicine pre-operative visit. This verbal consent is necessary to ensure that pre-operative baseline questionnaires can be administered. During this visit, the study protocol will also be explained to potential participants. In addition, a flyer detailing the study protocol will also be given to potential study participants. After verbal consent is obtained, the study team will allocate a study identification number, based on the study stratification schema, to the potential participant. Written consent will be obtained on the morning of surgery. The research pharmacy will allocate the participant into his/her assigned intervention group according to the randomization key associated with each study identification number. This key will be provided to the pharmacy by the study statisticians. All study team members, including the statisticians, and all clinical care providers will be blinded to the treatment group assignments. All subjects who provide verbal consent and complete the baseline assessment, but later decline participation in the study, or fail to give signed consent, will not be subject to any study-related follow-up or intervention. However their baseline assessment, which has already been acquired, may be used to identify factors that may predispose or bias patients toward enrollment. Patients who undergo secondary surgical procedures after admittance to the CSICU, and/or remain intubated longer than the 12 hours stipulated below, will not be subject to any further study procedures as they will no longer satisfy the primary inclusion and exclusion criteria.

**Primary inclusion criteria for patients and controls:** (1) age  $\geq$  60; (2) scheduled for a cardiac surgical procedure with planned post-operative admission to the CSICU for  $\geq$  24 hours; (3) scheduled same day surgical admission.

**Primary exclusion criteria for patients and controls:** (1) blind, deafness or the inability to speak English; (2) greater than 2 days of ICU admission in the month preceding the current surgical procedure; (3) renal and liver failure requiring dialysis or Child-Pugh score  $>$  5; (3) follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness); (4) previous cardiac surgery within 1 year of surgical procedure; (5) allergy to dexmedetomidine; (6) post-operative intubation  $>$  12 hours; (7) chronic therapy with benzodiazepines and/or

antipsychotics; (8) severe deficit due to structural or anoxic brain damage; (9) surgical procedure requiring total circulatory arrest.

**Primary objective drop criteria for patients and controls:** (1) Scheduled for a second surgical procedure during hospital stay.

**Intervention (dexmedetomidine-induced sleep vs. placebo).** After admission to the CSICU, rewarming, discontinuation of the sedative/anesthetic infusion and extubation of the airway, sedative medications will be administered as clinically indicated by the CSICU intensive care physician. Study patients admitted to the CSICU during the afternoon and extubated by 8:30 PM, would either receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) or placebo (normal saline over 40 minutes) every night throughout their CSICU stay. A sustained infusion of dexmedetomidine would never be administered for study related purposes. The targeted sleep induction time will be 9 PM. For the second start or later surgical cases, study patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would either receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) or placebo (normal saline over 40 minutes). The targeted sleep induction time will be within 30 minutes of extubation, with the earliest administration time being 9 PM. However, throughout the rest of the CSICU stay the sleep induction time will be targeted for 9 PM. In contrast, those patients who are admitted to the CSICU and remain intubated past past 2 AM will not begin study procedures until postoperative day 1, assuming they are extubated within 12 hours of admission to the CSICU. The maximum dose of dexmedetomidine that will be administered for any study participant will be 80mcg over a 40-minute period. Nighttime EEG may be obtained on all participants to enable sleep stage scoring in the spectral domain. The intraoperative EEG data acquisition system (Sedline) is a four-channel EEG device approved by MGH bioengineering. This device is currently used in all operating and procedural rooms at MGH for monitoring depth-of-anesthesia. For EEG monitoring in the ICU we will use the Compumedics Somte Portable PSG monitoring device.

Post cardiac surgical patients that are admitted to the CSICU have implanted temporary pacemakers and are also on a variety vasoactive medications (including but not limited to: norepinephrine, dobutamine, dopamine, and epinephrine) to maintain hemodynamic stability. Therefore, the administration of dexmedetomidine in these patients will not unduly compromise their cardiovascular status. However, patients with active bleeding necessitating surgical intervention will be excluded from the study.

**Outcome measures and variables of interest.** The primary outcome measure for this study is the incidence delirium in the CSICU on post-operative day 1. Secondary outcome measures include ICU- and hospital-delirium/coma-free days, length of hospital stay, 30-day mortality, 90-day mortality, and 180-day mortality. Variables of interest will include age, sex, years of formal education, race, ethnicity, marital status, , chronic disease burden (Charlson comorbidity index), cerebrovascular disease (Framingham Stroke Risk profile), physical function as assessed by NIH Patient Reported Outcomes Measurement Information System (PROMIS-29) questionnaires, organ failure (Sequential Organ Failure Assessment), length of cardiopulmonary bypass, presence of significant cardiac dysfunction (ejection fraction less than 35%), and sedative use in the ICU.

**Cognitive testing.** We will conduct delirium assessments twice daily (AM and PM with at least 6 hours between tests) beginning on post-operative day 1 using the Long- Confusion Assessment Method (CAM). Delirium assessments will be conducted up to day 3 or hospital discharge, whichever comes first. Patients who remain delirious past day 3 will be assessed until day 5 or hospital discharge, whichever comes first. For those patients who remain delirious past day 5, assessments will continue until day 7 or hospital discharge, whichever comes first.

**Other Cognitive Testing:** Cognitive decline will be estimated by taking into account the patient's baseline cognitive function and sleep quality before admission to the ICU, as assessed using the PROMIS-29, T-MOCA and PROMIS-4A questionnaires scored at recruitment, 1 month, 3 months, 6 months. The 3-D CAM will be administered at baseline. These questionnaires may be administered via email (RedCap) or regular mail, or phone call.

**Blood Draws:** For all patients, we will acquire peri-operative blood samples. This will enable us relate the serum metabolic/inflammatory profile to primary and secondary outcomes. For all study participants, blood sampling will be acquired as follows: (1) up to 40 ml of blood may be acquired at baseline on the day of surgery prior to the induction of general anesthesia (5-10ml for TSPO genetic profiling);(2) up to 20 ml of blood may be acquired at approximately 9 am of every ICU stay up to day 5. We may apply at least three distinct LC-

MS-based methods to study distinct plasma aliquots for each experimental sample.

**Anesthetic management and EEG data acquisition:** Intraoperatively, patients will receive standard anesthesia care in which the anesthesiologist uses age-adjusted drug dosing information, as well as heart rate, and blood pressure to set and titrate the anesthetic. This portion of the study will follow a strictly observational nature. EEG will be recorded per clinical practice in all patients using the 4-channel Sedline EEG machine that is installed in all operating rooms at MGH. In the ICU, EEG may be acquired through the Compumedics Portable PSG monitoring device.

**Other data.** A member of the study team will review the patient's bedside nursing log and clinical notes in the patient chart. A timeline of physiological data (obtained from continuously recorded clinical data in the CSICU), sedatives, analgesics, as well as any patient events will be recorded for later analysis in relation to outcome measures and nighttime spectral sleep stage scoring.

#### 4. DATA ANALYSIS PLAN

Data will be analyzed using an intention-to-treat approach defined as all randomized patients who receive an intervention. Continuous data will be described using median and interquartile range, and categorical data using frequencies and proportions. The primary outcome will be evaluated using logistic regression examining the presence or absence of delirium conditional on randomized group assignment. Any randomization imbalances, or other potential treatment effect modifiers will be further examined as covariates in sensitivity analyses. Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will use Pearson  $\chi^2$  tests to compare categorical variables between the 2 study groups and independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal care on mortality, CSICU and hospital lengths of stay, CSICU and hospital readmission rates. Kaplan-Meier survival curves will be used for graphical presentation of these time-to-event analyses and log-rank statistics to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients will be censored at the time of last contact alive or days from enrollment, whichever was first. Censoring for CSICU or hospital discharge readiness analyses will occur time of death or study withdrawal. Two-sided *P* values of .05 or less were considered to indicate statistical significance. Because missing data rarely occur entirely at random, we will assess the associations between patient characteristics with respect to missing data. If patients with at least one missing outcome value are different from those with complete outcomes data, we will use multiple imputation to assign values to missing risk factors and outcomes in regression modeling.

Metabolite concentrations will be log transformed to reduce heteroscedasticity of case-control differences. Metabolite levels will be compared in persons who developed delirium versus those who did not using two-tailed t tests. To screen these associations in the context of the balance of type-I and type-II errors, we will consider both FDR adjusted and Bonferroni-corrected *P* value thresholds. For metabolites meeting the less conservative FDR *P* value threshold, logistic regression analyses to estimate the OR of developing cognitive deficits will be performed at different metabolite values. Metabolites will be analyzed as continuous variables (log transformed and scaled to SD of 1), and regressions adjusted for age, sex, delirium assessment, CT-ICU length of stay, and surgical duration. To examine the unique predictive ability of these metabolites, we will conduct an exploratory stepwise logistic model including all metabolites meeting our threshold, and conduct cross-validation procedures to examine the internal consistency of these estimates. We will then construct a multimarker score based on the regression coefficients of the metabolites that were significant and consistent in our multivariable model, and then assess whether a model including clinical risk factors plus the multimarker panel improves delirium prediction compared with the model including clinical risk factors only.

All EEG data will be downloaded for off-line computational analysis. Data will be visualized and analyzed using signal processing and statistical algorithms available in MatLab, and using algorithms developed in house by the study investigators. To address hypothesis 3.1, we will employ multitaper power spectral analysis,<sup>21</sup> multitaper bivariate coherence analysis.<sup>18</sup> We will also perform phase-amplitude modulation between low and high frequency EEG components.<sup>21</sup> To address hypothesis 3.2, Segmentation of EEG recordings into burst and suppression periods will be performed in a semi-automated manner using an adaptation of previously described methods.<sup>22-24</sup> We will quantify the depth of burst suppression using the burst suppression probability (BSP), a number between 0 and 1, which describes the instantaneous probability of the EEG being in a state of suppression. A BSP value of 0 corresponds to a continuously active EEG with no

suppression, whereas a value of 1 corresponds to a completely isoelectric or suppressed EEG.

## 5. POWER ANALYSIS

The primary objective of this study is to detect a difference in the incidence of ICU delirium between the dexmedetomidine-induced sleep and normal care groups. Assuming a delirium event rate of 48%, a type I error of 0.05, and power of 0.80, an  $n = 150$  patients per group will enable us to detect an absolute difference 15% (i.e., 48% versus 33%). With respect to decreased morbidity and healthcare costs, this change represents a clinically meaningful difference. Therefore, we will recruit up to 150 patients per group.

## 6. REMUNERATION

Patients will be paid by check at the completion of the study for their participation as follows:

- \$15 for completion of questionnaires at each time-point (1, 3 and 6 months). Remuneration for all questionnaires completed by study participants will be processed 6 months after their surgery date. Thus, 1 check will be issued for all study questionnaires that are completed (i.e. \$45 for 3, \$30 for 2, and \$15 for 1 questionnaire).
  - Everyone who completes all questionnaire time-points will be enrolled in a raffle to win 1 of 3 iPads.

## 7. RISK AND DISCOMFORT

**Dexmedetomidine risks:** The risks involved in the administration of dexmedetomidine include nausea, xerostomia, atrial fibrillation, and transient hypertension during drug loading. The significant risks involved are directly related to a drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. Rare case reports of sinus arrest in instances of rapid drug administration and in patients with a high resting vagal tone have also been described. Drug discontinuation, dose reduction, or the use of vasoactive substances causes a return of these hemodynamic parameters to baseline. All subject hemodynamic parameters will be continuously monitored to ensure that appropriate medical intervention will be instituted for any clinically significant hypotensive or bradycardic episodes. In addition, most of our study subjects will have temporary pacemakers in place for routine post surgical heart-rate management. Since dexmedetomidine maintains the respiratory rate and we are only administering a one-time dose (similar to our recently completed proof of concept study in healthy volunteers; NCT01485393), there is no concern for respiratory compromise.

**EEG risks:** The risks associated with EEG electrodes are redness and irritation at placement site.

**Psychological risks:** Psychological risks include the possibility of claustrophobia within the scanner.

**Questionnaire risks:** Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning.

**Data risks:** Procedures are in place to reduce the likelihood of a breach of confidentiality including the de-identification of data and storage of data only on partners approved devices/portals. However, there is a small risk that people outside of this study may be exposed to information about study subjects.

## 8. POTENTIAL BENEFITS

Subjects will have no direct benefit from taking part in this study. Findings from these studies will help advance our understanding of the pathophysiology of delirium. In particular, this project will assess the role of sleep induction and neuroinflammation in the establishment and/or maintenance of delirium. As such, we envision that in the future the information obtained from the proposed research will enhance the diagnosis and management of delirium.

## 9. MONITORING AND QUALITY ASSURANCE

No identifiers other than study ID's will be included in the dataset. Thus, all data will be deidentified and data will be stored on password protected partners computers and cluster for off-line analysis. The proposed study will be monitored for safety, with monthly staff meetings reviewing adverse events and treatment outcomes and directly reporting any adverse events. The PI will also routinely monitor and assure the validity and integrity of collected data and adherence to the IRB-approved protocol. The trained staff members who carry out the procedures will also carefully monitor the study throughout its duration. The team will evaluate the progress of the study, verify that the rights and well being of the subjects are protected, verify that the reported



1 study data are accurate, complete and verifiable from source documents, and the conduct of the study is in  
2 compliance with the approved protocol and amendments. Outcome monitoring and adverse events will all be  
3 reported through appropriate channels of the Human Studies Committee. A DSMB will also oversee this study.

4 Unanticipated problems involving risks to subjects or others including adverse events will be reported to  
5 the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines, as  
6 well as the RDRC within 5 days.  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## References

1. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. Washington, D.C.: American Psychiatric Association; 2013.
2. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2013;21:1190-222.
3. O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *Journal of the American Geriatrics Society* 1997;45:174-8.
4. McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? *Journal of the American Geriatrics Society* 2003;51:1539-46.
5. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *Jama* 1990;263:1097-101.
6. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *The New England journal of medicine* 2013;369:1306-16.
7. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nature reviews Neurology* 2009;5:210-20.
8. Gross AL, Jones RN, Habtemariam DA, et al. Delirium and Long-term Cognitive Trajectory Among Persons With Dementia. *Archives of internal medicine* 2012;172:1324-31.
9. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Archives of internal medicine* 2008;168:27-32.
10. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Critical care medicine* 2001;29:1370-9.
11. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *Journal of the American Geriatrics Society* 2010;58:643-9.
12. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta neuropathologica* 2010;119:737-54.
13. Norden DM, Godbout JP. Review: microglia of the aged brain: primed to be activated and resistant to regulation. *Neuropathology and applied neurobiology* 2013;39:19-34.
14. Cunningham C. Systemic inflammation and delirium: important co-factors in the progression of dementia. *Biochemical Society transactions* 2011;39:945-53.
15. Ingiosi AM, Opp MR, Krueger JM. Sleep and immune function: glial contributions and consequences of aging. *Current opinion in neurobiology* 2013;23:806-11.
16. Vacas S, Degos V, Feng X, Maze M. The neuroinflammatory response of postoperative cognitive decline. *British medical bulletin* 2013;106:161-78.
17. Zhu B, Dong Y, Xu Z, et al. Sleep disturbance induces neuroinflammation and impairment of learning and memory. *Neurobiology of disease* 2012;48:348-55.

18. Purdon PL, Pavone KJ, Akeju O, et al. The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. *British journal of anaesthesia* 2015;115 Suppl 1:i46-i57.
19. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Annals of internal medicine* 1990;113:941-8.
20. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *Jama* 2001;286:2703-10.
21. Purdon PL, Pierce ET, Mukamel EA, et al. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci U S A* 2013;110:E1142-51.
22. Brandon Westover M, Shafi MM, Ching S, et al. Real-time segmentation of burst suppression patterns in critical care EEG monitoring. *Journal of neuroscience methods* 2013;219:131-41.
23. Lewis LD, Ching S, Weiner VS, et al. Local cortical dynamics of burst suppression in the anaesthetized brain. *Brain : a journal of neurology* 2013;136:2727-37.
24. Brandon Westover M, Ching S, Kumaraswamy VM, et al. The human burst suppression electroencephalogram of deep hypothermia. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 2015;126:1901-14.
25. Chemali JJ, Wong KF, Solt K, Brown EN. A state-space model of the burst suppression ratio. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference* 2011;2011:1431-4.
26. Chemali J, Ching S, Purdon PL, Solt K, Brown EN. Burst suppression probability algorithms: state-space methods for tracking EEG burst suppression. *Journal of neural engineering* 2013;10:056017.

# BMJ Open

## Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020316.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Dec-2017
Complete List of Authors:	<p>Shelton, Kenneth; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Qu, Jason; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Bilotta, Federico; University of Rome "Sapienza", Anesthesiology</p> <p>Brown, Emery; Massachusetts Institute of Technology Institute for Medical Engineering and Science; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Cudemus, Gaston; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>D'Alessandro, David; Massachusetts General Hospital, Department of Surgery, Division of Cardiac Surgery</p> <p>Deng, Hao; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>DiBiasio, Alan; Massachusetts General Hospital, Department of Pharmacy</p> <p>Gitlin, Jacob; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Hahm, Eunice; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Hobbs, Lauren; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Houle, Timothy T. ; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Ibala, Reine; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Loggia, Marco; Massachusetts General Hospital, Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology</p> <p>Pavone, Kara; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Shaefi, Shahzad; Beth Israel Deaconess Medical Center, Department of Anesthesia and Critical Care</p> <p>Tolis, George; Massachusetts General Hospital, Department of Surgery, Division of Cardiac Surgery</p> <p>Westover, Brandon; Massachusetts General Hospital, Department of Neurology</p> <p>Akeju, Oluwaseun; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p>
<b>Primary Subject	Intensive care



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Heading</b> :	
Secondary Subject Heading:	Anaesthesia, Cardiovascular medicine, Neurology
Keywords:	Delirium, Biomimetic sleep, Dexmedetomidine, Cardiac surgery < SURGERY, Patient reported outcomes

SCHOLARONE™  
Manuscripts

For peer review only

1  
2  
3 **Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep**  
4 **(MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial**  
5  
6  
7

8 KT Shelton<sup>1</sup>, J Qu<sup>1</sup>, F Bilotta<sup>2</sup>, EN Brown<sup>1,3</sup>, G Cudemus<sup>1</sup>, DA D'Alessandro<sup>4</sup>, H Deng<sup>1</sup>, A  
9 DiBiasio<sup>5</sup>, J Gitlin<sup>1</sup>, EY Hahm<sup>1</sup>, LE Hobbs<sup>1</sup>, TT Houle<sup>1</sup>, R Ibalá<sup>1</sup>, M Loggia<sup>6</sup>, KJ Pavone<sup>1</sup>, S  
10 Shaefi<sup>7</sup>, G Tolis<sup>4</sup>, MB Westover, O Akeju\*<sup>1</sup>  
11

12 **Affiliations:**

13 <sup>1</sup> Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General  
14 Hospital, Boston MA, 02114

15 <sup>2</sup> Department of Anaesthesia and Critical Care Medicine, "Sapienza" University Rome

16 <sup>3</sup> Institute for Medical Engineering and Sciences, Massachusetts Institute of Technology,  
17 Cambridge MA, 02139

18 <sup>4</sup> Department of Surgery, Division of Cardiac Surgery, Massachusetts General Hospital, Boston  
19 MA, 02114

20 <sup>5</sup> Department of Pharmacy, Massachusetts General Hospital, Boston MA, 02114

21 <sup>6</sup> Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology,  
22 Massachusetts General Hospital, Boston MA, 02114

23 <sup>7</sup> Department of Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, Boston  
24 MA, 02215

25 <sup>8</sup> Department of Neurology, Massachusetts General Hospital, Boston MA, 02114  
26  
27  
28  
29

30 \*To whom correspondence should be addressed

31 Oluwaseun Johnson-Akeju

32 Massachusetts General Hospital

33 Department of Anesthesia, Critical Care and Pain Medicine

34 55 Fruit St

35 Boston, MA 02114

36 USA

37 oluwaseun.akeju@mgh.harvard.edu  
38  
39  
40  
41  
42  
43

44 **Version:** December 2, 2017

45 **Amendment 2:**

46 NCT02856594

47 Funding for the MINDDS trial is through a grant awarded by the National Institutes on Aging  
48 (R01 AG053582).  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59  
60

**STUDY TEAM ROSTER****Principal****Investigator:****Oluwaseun Johnson-Akeju, M.D., M.M.Sc.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-724-2000  
oluwaseun.akeju@mgh.harvard.edu

**Co-Investigators:****Federico Bilotta, MD**

University of Rome 'La Sapienza'  
Department of Anesthesiology  
Piazzale Aldo Moro,  
5, 00185 Roma, Italy  
339 33 708 22  
bilotta@tiscali.it

**Emery N. Brown, M.D., Ph.D.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-324-1880  
enb@neurostat.mit.edu

**Gaston Cudemus, M.D.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-726-9149  
gcudemus@mgh.harvard.edu

**David D'Alessandro, M.D.**

Massachusetts General Hospital

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 Department of Surgery  
4 Division of Cardiac Surgery  
5 Cox Building 644  
6 Boston, MA 02114  
7 United States  
8 617-726-8841  
9 dadalessandro@mgh.harvard.edu  
10  
11

12  
13 **Hao Deng, M.D., M.P.H.**

14 Massachusetts General Hospital  
15 Department of Anesthesiology  
16 55 Fruit Street  
17 Gray/Jackson 444  
18 Boston, MA 02114  
19 United States  
20 617-643-6757  
21 hdeng1@mgh.harvard.edu  
22  
23

24 **Alan DiBiasio, B.S. Pharm**

25 Massachusetts General Hospital  
26 Department of Pharmacy,  
27 55 Fruit St  
28 Gray/Bigelow 005  
29 Boston, MA 02114  
30 United States  
31 617-724-1270  
32 adibiasio@partners.org  
33  
34  
35

36 **Jacob A Gitlin, B.S.**

37 Massachusetts General Hospital  
38 Department of Anesthesiology  
39 55 Fruit Street  
40 Gray/Jackson 444  
41 Boston, MA 02114  
42 United States  
43 617-724-2000  
44 jgitlin1@partners.org  
45  
46

47 **Eunice Y Hahm, B.S**

48 Massachusetts General Hospital  
49 Department of Anesthesiology  
50 55 Fruit Street  
51 Gray/Jackson 444  
52 Boston, MA 02114  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

1  
2  
3 United States  
4 617-724-2000  
5 ehahm@mgh.harvard.edu  
6  
7

8 **Lauren E. Hobbs, M.S.**

9 Massachusetts General Hospital  
10 Department of Anesthesiology  
11 55 Fruit Street  
12 Gray/Jackson 444  
13 Boston, MA 02114  
14 United States  
15 617-724-9857  
16 lehobbs@mgh.harvard.edu  
17

18 **Timothy Houle, Ph.D.**

19 Massachusetts General Hospital  
20 Department of Anesthesiology  
21 55 Fruit Street  
22 Gray/Jackson 444  
23 Boston, MA 02114  
24 United States  
25 617-724-2111  
26 thoule1@mgh.harvard.edu  
27  
28

29 **Reine Ibala, B.S.**

30 Massachusetts General Hospital  
31 Department of Anesthesiology  
32 55 Fruit Street  
33 Gray/Jackson 444  
34 Boston, MA 02114  
35 United States  
36 617-724-2000  
37 ribala@mgh.harvard.edu  
38  
39

40 **Marco L. Loggia, Ph.D.**

41 Massachusetts General Hospital  
42 Department of Radiology  
43 149 13th Street  
44 CNY - Building 149  
45 Charlestown, MA 02129  
46 United States  
47 617-643-7267  
48 marco.loggia@mgh.harvard.edu  
49  
50

51 **Jason Qu, M.D.**

52 Massachusetts General Hospital  
53 Department of Anesthesiology  
54 55 Fruit Street

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

1  
2  
3 Gray/Jackson 444  
4 Boston, MA 02114  
5 United States  
6 617-643-4401  
7 jqu@partners.org  
8

9  
10 **Kara J. Pavone, B.S., B.S.N., R.N.**

11 Massachusetts General Hospital  
12 Department of Anesthesiology  
13 55 Fruit Street  
14 Gray/Jackson 444  
15 Boston, MA 02114  
16 United States  
17 617-724-9857  
18 kpavone@mgh.harvard.edu

19 **Shahzad Shaefi, M.D., MPH**

20 Beth Israel Deaconess Medical Center  
21 Department of Anesthesia and Critical Care  
22 330 Brookline Avenue,  
23 Feldberg 407  
24 Boston, MA 02215  
25 United States  
26 617-667-3112  
27 sshaefi@bidmc.harvard.edu  
28

29  
30 **Kenneth Shelton, M.D.**

31 Massachusetts General Hospital  
32 Department of Anesthesiology  
33 55 Fruit Street  
34 Gray/Jackson 444  
35 Boston, MA 02114  
36 United States  
37 617-726-0917  
38 kshelton2@partners.org  
39  
40

41  
42 **George Tolis, M.D.**

43 Massachusetts General Hospital  
44 Department of Surgery  
45 Division of Cardiac Surgery  
46 55 Fruit Street  
47 Cox Building 654  
48 Boston, MA 02114  
49 United States  
50 617-643-9280  
51 gtolis@partners.org  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

**M. Brandon Westover, MD, PhD**

Massachusetts General Hospital  
 Department of Neurology  
 55 Fruit Street  
 Boston, MA 02114  
 United States  
 617-726-3311  
 mwestover@mgh.harvard.edu

<b>Primary Registry and Trial Identifying Number</b>	<b>ClinicalTrials: NCT02856594</b>
<b>Date of Registration</b>	July 29 2016
<b>Secondary Identifying Numbers</b>	IRB ID#: 2016 P000742
<b>Source(s) of Monetary Support</b>	National Institute on Aging Grant (Award Reference Number R01 AG053582-01)
<b>Primary Sponsor</b>	Department of Anesthesiology, Critical care and Pain Medicine Massachusetts General Hospital Boston, MA 02114
<b>Contact name</b>	Oluwaseun Akeju, M.D., M.M.Sc oluwaseun.akeju@mgh.harvard.edu 617-724-2000 Department of Anesthesiology, Critical care and Pain Medicine Massachusetts General Hospital 55 Fruit Street Gray/Jackson 444 Boston, MA 02114 United States
<b>Contact for Scientific Queries</b>	Oluwaseun Akeju, M.D., M.M.Sc oluwaseun.akeju@mgh.harvard.edu 617-724-2000 Department of Anesthesiology Massachusetts General Hospital 55 Fruit Street Gray/Jackson 444 Boston, MA 02114 United States

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1		
2		
3		
4	<b>Public Title</b>	Protocol for the Minimizing ICU Neurological
5		Dysfunction with Dexmedetomidine-induced Sleep
6		(MINDDS) Trial
7		
8	<b>Scientific Title</b>	Protocol for the Minimizing ICU Neurological
9		Dysfunction with Dexmedetomidine-induced Sleep
10		(MINDDS) Trial: a Randomized, Double blind, Parallel-
11		arm, Placebo-controlled Clinical Trial
12		
13	<b>Countries of Recruitment</b>	United States
14		
15	<b>Health Condition(s) or Problem(s) Studied</b>	Postoperative delirium, predictors of delirium
16		
17		
18		
19	<b>Intervention(s)</b>	Trial arm 1: Dexmedetomidine-induced Sleep Group
20		(primary intervention)
21		Post cardiac surgical patients admitted to the cardiac
22		surgical intensive care unit (CSICU) and extubated at
23		least 30 minutes prior to 8:30 PM would receive a
24		sleep induction dose of dexmedetomidine (1mcg/kg
25		over 40 minutes; maximum administered dose of
26		80mcg at any one instance) at 9 PM every night
27		throughout their CSICU stay. Trial patients admitted to
28		the CSICU and extubated after 8:30 PM, but before 2
29		AM, would receive a sleep induction dose of
30		dexmedetomidine within 30 minutes of extubation.
31		However, throughout the rest of the CSICU stay the
32		dexmedetomidine administration time will be targeted
33		for 9 PM. Trial patients admitted to the CSICU and
34		remain intubated past 2 AM will begin trial procedures
35		the following day, assuming they are extubated within
36		12 hours of admission to the CSICU.
37		
38		Trial arm 2: Placebo Control Group.
39		Post cardiac surgical patients admitted to the CSICU
40		and extubated at least 30 minutes prior to 8:30 PM
41		would receive placebo (intravenous normal saline over
42		40 minutes) at 9 PM every night throughout their
43		CSICU stay. Trial patients admitted to the CSICU and
44		extubated after 8:30 PM, but before 2 AM, would
45		receive the placebo infusion of normal saline within 30
46		minutes of extubation. However, throughout the rest of
47		
48		
49		
50		
51		
52		
53		
54		

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.



the CSICU stay the placebo administration time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU.

### Key Inclusion, Exclusion and Objective Drop Criteria

#### Inclusion Criteria

1. Age  $\geq$  60
2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for  $\geq$  24 hours
3. Scheduled same day surgical admission

#### Exclusion Criteria

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score  $>$  5
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit due to structural or anoxic brain damage
9. Surgical procedures requiring total circulatory arrest

#### Objective Drop Criteria

1. Scheduled for a second surgical procedure during hospital stay
2. Post-operative intubation  $>$  12 hours

### Trial Type

#### Interventional

Allocation: Randomized

Intervention model: Parallel assignment

Blinding: Clinicians blinded to intervention, subject blinded to intervention, primary outcome assessor blinded to intervention

Assignment: Parallel

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

	Primary purpose: Prevention
<b>Date of First Enrollment</b>	March, 2017
<b>Target Sample Size</b>	Recruiting until 370 patients receive the study intervention on Post Operative Day 0.
<b>Recruitment Status</b>	Enrolling
<b>Primary Outcome(s)</b>	Outcome name: Incidence of postoperative delirium Method of measurement: The Long Confusion Assessment Method Time points of interest: Postoperative day 1
<b>Key Secondary Outcomes</b>	Outcome name: ICU and hospital delirium/coma-free days Method of measurement: Delirium assessment with: The Long Confusion Assessment Method Time points of interest: Up until postoperative day 3 if no delirium. Up until postoperative day 5 if delirium exhibited but resolved. Up until postoperative day 7 or discharge if delirium unresolved by postoperative day 5. Outcome name: Severity of Delirium Method of measurement: The Long Confusion Assessment Method Time points of interest: Up until postoperative day 3 if no delirium. Up until postoperative day 5 if delirium exhibited but resolved. Up until postoperative day 7 or discharge if delirium unresolved by postoperative day 5. Outcome name: Date of Hospital Discharge / Length of Hospital Stay Method of measurement: Medical record review

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 Time points of interest: Up until hospital discharge  
4

5 Outcome name: 30-day, 90-day, and 180-day  
6 mortality  
7

8 Method of measurement: Medical record review  
9

10 Time points of interest: 30 days, 90 days and 180  
11 days postoperatively  
12

13 Outcome name: Postoperative cognitive status  
14

15 Method of measurement: Abbreviated Montreal  
16 Cognitive Assessment, 3D-CAM and PROMIS-29  
17 applied cognition abilities questionnaire  
18

19 Time points of interest: 30 days, 90 days and 180  
20 days postoperatively  
21

22 Outcome name: Postoperative health related quality  
23 of life  
24

25 Method of measurement: PROMIS-29 physical  
26 function, global health, pain interference  
27 questionnaires, and sleep questionnaire  
28

29 Time points of interest: 30 days, 90 days and 180  
30 days postoperatively  
31  
32

33 **Authors' contributions:** Authorship for this trial will be given to key personnel involved in trial  
34 design, recruitment, data collection, and data analysis. There are no publication restrictions and  
35 no professional writers will be involved in the generation of the manuscript. KTS, JQ, GC, HD,  
36 JAG, EYH, LEH, TTH, RI, KJP, and OA were responsible for conceptualizing trial design. JQ  
37 managed patient safety protocol. EYH, JAG, RI, and LH were responsible for recruitment,  
38 enrolment, and data collection. KTS, JQ, FB, ENB, GC, DAD, HD, AD, JAG, EYH, LEH, TTH,  
39 RI, ML, KJP, SS, GT, MBW, and OA have critically revised the MINDDS protocol and approved  
40 the final version. All authors agree to be accountable for the accuracy and integrity of all aspects  
41 of the MINDDS trial.  
42  
43  
44  
45  
46  
47

48 **Conflict of interest statement:** OA and ENB have a provisional patent application describing  
49 the use of alpha-2 agonists for promoting N3 sleep. All other authors have no interests to  
50 declare.  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

## ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

### Principal Investigator:

Oluwaseun Akeju, M.D., M.M.Sc.

Responsibilities include: design and conduct of the MINDDS trial, preparation of protocol and revisions, organization of steering committee meetings, and publication of trial reports.

### Steering Committee:

Oluwaseun Akeju, M.D., MMSc	Gaston Cudemus, M.D. Marco L Loggia, Ph.D.	Ken Shelton, M.D. Brandon M Westover, M.D., Ph.D.
Federico Bilotta, MD	Kara Pavone, B.SN., R.N	
Alan DiBiasio, Pharm.D	Jason Qu, M.D.	
Tim Houle, Ph.D	Shahzad Shaefi, M.D., MPH	

Responsibilities include: agreement of final protocol, reviewing progress of trial and if necessary, conducting changes to the protocol, coordinating with principal investigator, and communicating with trial management committee.

### Trial Management Committee:

Oluwaseun Akeju, M.D, M.M.Sc.  
Tim Houle, Ph.D.  
Lauren E Hobbs, M.S.  
Reine Ibalá, B.S.  
Eunice Hahm, B.S.  
Jacob Gitlin, B.S.  
Kara Pavone, B.S.N, R.N.  
Jason Qu, M.D.  
Ken Shelton, M.D.

Responsibilities include: trial planning, organization of steering committee meetings, reporting SAEs (Serious Adverse Events) to Partners Healthcare IRB (Institutional Review Board), maintaining REDCap electronic database, reporting to steering committee, conducting data verification, recruitment, randomization, and follow-up of trial participants

### Data Management Committee:

Hao Deng, M.D., M.P.H.  
Tim Houle, Ph.D.

Responsibilities include: statistical design of trial, data verification.

### Data Adjudication Committee:

Oluwaseun Akeju, M.D., M.M.Sc.  
Shahzad Shaefi, M.D., MPH

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 Brandon M Westover, M.D., Ph.D.  
4

5 Responsibilities include: regularly reviewing delirium assessments, contacting trial management  
6 committee, retraining researchers if necessary.  
7

8  
9 **Data and Safety Monitoring Committee:**

10 Wie Chao, M.D., Ph.D. - University of Maryland School of Medicine

11 Jesse Ehrenfeld, M.D.,M.P.H. -Vanderbilt University Medical Center

12 Michael Gropper, M.D., Ph.D. - University of California San Francisco

13 Keith A. Jones, M.D. - The University of Alabama at Birmingham  
14

15 Responsibilities include: reviewing and evaluating the trial data to ensure participant safety, trial  
16 conduct, progress, and efficacy, and making recommendations regarding the continuation,  
17 modification, and termination of the trial.  
18

19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

## Abstract

**Introduction:** Delirium, which is prevalent in post cardiac surgical patients, is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder. The pathophysiology of delirium remains poorly understood. However, basic science and clinical studies suggest that sleep disturbance may be a modifiable risk factor for the development of delirium. Dexmedetomidine is a  $\alpha_2$  adrenergic receptor agonist medication that patterns the activity of various arousal nuclei similar to sleep. A single nighttime loading dose of dexmedetomidine promotes non-rapid eye movement sleep stages N2 and N3 sleep. This trial hypothesizes dexmedetomidine-induced sleep as pre-emptive therapy for postoperative delirium.

**Methods and Analysis:** The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is a 370-patient block-randomized, placebo-controlled, double-blinded, single-site, parallel-arm superiority trial. Patients over 60 years old, undergoing cardiac surgery with planned cardiopulmonary bypass, will be randomized to receive a sleep inducing dose of dexmedetomidine or placebo. The primary outcome is the incidence of delirium on postoperative day 1, assessed with the Confusion Assessment Method by staff blinded to the treatment assignment. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 370 patients receive the study intervention on post-operative day 0. Secondary outcomes will be evaluated by in-person assessments and medical record review for in-hospital end points, and by telephone interview for 30-day, 90-day, and 180-day end points. All trial outcomes will be evaluated using an intention-to-treat analysis plan. Hypothesis testing will be performed using a two-sided significance level (type I error) of  $\alpha=0.05$ . Sensitivity analyses using the actual treatment received will be performed and compared with the intention-to-treat analysis results.

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 Additional sensitivity analyses will assess the potential impact of missing data due to loss of  
4 follow-up.  
5  
6

7  
8 **Ethics and dissemination:** The Partners Human Research Committee approved the MINDDS  
9 trial. Recruitment began in March 2017. Dissemination plans include presentations at scientific  
10 conferences, scientific publications, and popular media.  
11  
12

13  
14  
15 **Registration details:** NCT02856594.  
16

### 17 **Strengths and limitations**

- 18 • The treatment protocol is based on a plausible biological mechanism suggesting that  
19 biomimetic sleep may reduce the incidence of delirium.  
20
- 21 • The treatment protocol is straightforward and will allow the results to be generalized  
22 to patients across a range of care settings.  
23
- 24 • Collection of patient-centered outcomes data, including measures of functional  
25 independence, at up to 180-days will provide insight into the relationship between the  
26 trial intervention and meaningful patient end points.  
27
- 28 • Risk factors and pathophysiological mechanisms of delirium will be explored in  
29 separate sub-studies.  
30
- 31 • Delirium is a fluctuating disorder that may occasionally be missed despite rigorous  
32 and validated assessment methods.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

## Introduction

Delirium, which is prevalent in post cardiac surgical patients,<sup>1</sup> is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition that is not explained by a preexisting neurocognitive disorder.<sup>2</sup> Although previously reported associations between delirium and increased mortality are debatable,<sup>3</sup> delirium remains a leading cause of preventable morbidity in hospitalized elderly patients.<sup>3,4</sup> The morbidity associated with delirium is estimated to result in increased healthcare costs of approximately \$16,000-\$64,000 per patient annually. Increasing age and pre-existing cognitive impairment are key predisposing factors for delirium. Despite its impact, there are no definitive pharmacological preventative strategies for delirium. However, basic science and clinical studies suggest that sleep disturbances may be a modifiable risk factor for the development of delirium.

Sleep is a natural occurring state of decreased arousal that is crucial for normal cardiovascular, immune and cognitive function. Sleep deprivation, which is associated with increased pro-inflammatory cytokine levels including interleukin-6,<sup>5-7</sup> precedes the onset of delirium in some patients.<sup>8,9</sup> A recent investigation linking brain activity of microglia, astrocytes, interleukin-6 and delirium in humans,<sup>10</sup> suggests a mechanistic link between sleep deprivation, brain inflammation, and delirium. Further, conditions associated with delirium are characterized by activation of the inflammatory cascade with acute release of inflammatory mediators.<sup>11-25</sup> Increasing age is a significant risk factor for the development of delirium. Notably, aging is associated with activated brain glia cell.<sup>4, 26</sup> Following a systemic challenge such as critical illness, these activated glia have been suggested to facilitate an exaggerated neuroinflammatory state that predisposes to delirium.<sup>4, 26-28</sup>

Sleep disturbance is a hallmark feature of the postoperative period,<sup>29-33</sup> and pharmacological induction of altered arousal states that are neurophysiologically

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.



1  
2  
3 indistinguishable from sleep, termed biomimetic sleep, may represent a preventative strategy for  
4 the development of postoperative delirium.<sup>34 35</sup> However, commonly administered sedative  
5 drugs, most of which modulate the  $\gamma$  amino butyric acid A (GABA<sub>A</sub>) receptor induce altered  
6 arousal states that are neurophysiologically distinct from sleep.<sup>34 35</sup> This neurophysiological  
7 distinction from sleep (i.e. frontal beta oscillations, frontal alpha oscillations, burst suppression,  
8 isoelectricity)<sup>34-41</sup> may explain why current sedative medications that modulate GABA<sub>A</sub> receptors  
9 are not delirium sparing. Rather, neural circuit dysfunction in sensory, memory encoding, and  
10 cognitive processing circuits may in part explain why these medications are independent risk  
11 factors for the development of delirium.<sup>34 42</sup>

12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22 Dexmedetomidine is a  $\alpha$ 2a adrenergic receptor agonist medication that patterns the  
23 activity of various arousal nuclei similar to sleep.<sup>43-47</sup> Neurophysiologically, a continuous infusion  
24 of dexmedetomidine produces spindle and slow-delta oscillations.<sup>34 39 48</sup> This oscillatory dynamic  
25 shares features with non-rapid eye movement (REM) sleep stage N2 sleep.<sup>34 39 49 50</sup> Consistent  
26 with the hypothesis that the neurophysiological approximation of sleep may prevent delirium, the  
27 dexmedetomidine-infusion N2 sleep stage (with absent non-REM stages N1, N3 and REM  
28 sleep) has been associated with a reduced incidence of delirium in critically ill patients.<sup>51-54</sup>  
29 Instead of a continuous drug infusion, we recently found that a single nighttime dose of  
30 dexmedetomidine preserves normal sleep cycling.<sup>35</sup> This drug administration paradigm  
31 promotes non-REM stage N3 sleep. Notably, N3 sleep is associated with improved cognition  
32 and synaptic plasticity.<sup>55-63</sup>

33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46 A neurophysiologically principled approach to pharmacologically promote sleep may  
47 reduce significantly the incidence of delirium in hospitalized patients. The primary objective of  
48 the MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep)  
49 trial is to evaluate dexmedetomidine-induced sleep as a pharmacological preventative strategy

50  
51  
52  
53  
54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.

1  
2  
3 for delirium, and to characterize the impact of delirium prevention on patient-centered outcomes  
4 such as functional recovery. In separate sub-studies, risk factors and pathophysiological  
5 mechanisms of delirium will be explored using: 1) unbiased serum metabolic, proteomic, and  
6 extracellular vesicular profiling; 2) power spectral analyses of intraoperative and CSICU  
7 electroencephalogram dynamics; and, 3) integrated positron emission tomography/magnetic  
8 resonance imaging of [<sup>11</sup>C] PBR28.  
9  
10  
11  
12  
13  
14

### 15 16 **Trial objectives**

17  
18 Our primary hypothesis is that dexmedetomidine-induced sleep will result in a reduced  
19 incidence of delirium. Our intervention and control groups will be comprised of extubated  
20 cardiac surgical intensive care unit (CSICU) patients, because their relative homogeneity in  
21 terms of surgical procedures (i.e. cardiac surgery performed on cardiopulmonary bypass),  
22 anesthetic management, and systemic inflammatory response represents a unique opportunity  
23 to study the mechanisms underlying delirium, while limiting confounding factors that may  
24 otherwise be encountered in heterogeneous patients  
25  
26  
27  
28  
29  
30  
31  
32

### 33 **Methods and analysis**

#### 34 **Trial design**

35  
36 We will enroll 370 patients over a period of three years into a randomized, controlled,  
37 double-blinded, single-site, parallel-arm superiority trial. Our primary outcome is the incidence of  
38 delirium on postoperative day 1 upon administration of the study intervention. To ensure that the  
39 study is appropriately powered for the primary outcome measure, patients will be recruited and  
40 randomized into the study until 370 patients receive the study intervention on post-operative day  
41 0. Trial end points will be assessed via in-person interview (during hospitalization), medical  
42 record review, and telephone interview (after hospital discharge). The primary and secondary  
43 outcomes of delirium will be assessed via in-person interviews, which will be performed in the  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

1  
2  
3 morning and afternoon with approximately 6 hours between interviews. All outcomes, including  
4 those obtained post discharge, will be assessed in a blinded fashion.  
5  
6

### 7 **Eligibility criteria**

#### 8 **Inclusion criteria**

- 9 1. Age  $\geq$  60
- 10 2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the  
11 CSICU for  $\geq$  24 hours
- 12 3. Scheduled same day surgical admission

#### 13 **Exclusion criteria**

- 14 1. Blindness, deafness or the inability to speak English
- 15 2. Greater than 2 days of ICU admission in the month preceding the current surgical  
16 procedure
- 17 3. Renal and liver failure requiring dialysis or Child-Pugh score  $>$  5
- 18 4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
- 19 5. Previous cardiac surgery within 1 year of surgical procedure
- 20 6. Allergy to dexmedetomidine
- 21 7. Chronic therapy with benzodiazepines and/or antipsychotics
- 22 8. Severe neurological deficit
- 23 9. Surgical procedure requiring total circulatory arrest

#### 24 **Objective Drop Criteria**

- 25 1. Scheduled for a second surgical procedure during hospital stay
- 26 2. Postoperative intubation  $>$  12 hours

27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58

## Baseline assessment

Patients will undergo a pre-randomization assessment that includes a brief medical record review, and evaluation the following:

1. Baseline cognitive function using the abbreviated Montreal Cognitive Assessment
2. Presence of delirium at the time of interview, as measured by the 3-min assessment for Confusion Assessment Method-defined delirium (3D-CAM)
3. Physical function with the PROMIS SF v1.2 -Physical function 8b
4. General health with the PROMIS SF v1.1- Global
5. Pain with the PROMIS SF v1.0- Pain Interference 8a
6. Applied cognition with the PROMIS v1.0- Applied Cognition Abilities SF 8a
7. Baseline sleep quality with the PROMIS-4A

## Intervention

We will randomly allocate patients to receive placebo or dexmedetomidine nightly during their CSICU stay. All clinical care during preoperative, intraoperative and postoperative periods will follow normal standard of care. However, trial patients admitted to the CSICU and extubated at least 30 minutes prior to 8.30 PM would receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8.30 PM, but before 2 AM, would receive a sleep induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the rest of the CSICU stay the sleep induction time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU. The maximum dexmedetomidine dose that will be administered at any one instance is 80 mcg. Clinicians will be asked to refrain from routinely administering dexmedetomidine to patients in the operating

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 room and in the CSICU. Otherwise, all other care decisions will be at the discretion of the  
4  
5 clinical care team.

## 7 **Outcomes**

### 9 **Primary outcome**

10  
11 The primary outcome measure for this trial is the incidence delirium in the CSICU on  
12  
13 postoperative day 1. Delirium assessments will be conducted twice daily (AM and PM with at  
14  
15 least 6 hours between tests) beginning on postoperative day 1 using the Long Confusion  
16  
17 Assessment Method (CAM).<sup>64 65</sup> Trial staff blinded to treatment assignments will perform the  
18  
19 delirium assessments. A combination of the 3D-CAM and the abbreviated Montreal cognitive  
20  
21 assessment conducted at baseline includes all the cognitive domains that are captured by the  
22  
23 long-CAM. Thus, long-CAM results will be benchmarked against these baseline data for delirium  
24  
25 scoring (i.e. change from baseline). Patients who elect to withdraw from the study during their  
26  
27 hospital stay will be re-approached by the study team within 8-24 hours of study withdrawal. The  
28  
29 study team member will elicit the reason for study discontinuation and confirm the withdrawal  
30  
31 decision. This visit serves to ensure that the withdrawal decision was made during an informed  
32  
33 and non-delirious cognitive state. In the event that a patient finds it difficult to complete an  
34  
35 assessment (i.e. pain, clinical intervention), only the long-CAM domains necessary to dispel the  
36  
37 presence of delirium will be assessed (i.e. acute onset, inattention, disorganized thinking and  
38  
39 altered level of consciousness). Patients who cannot complete this shortened assessment will  
40  
41 be re-approached several hours later. Long-CAM assessments for patients who are reintubated  
42  
43 for clinical care or for further surgical management will be considered missing data.

### 47 **Secondary outcomes (in-hospital)**

48  
49 Blinded trial staff will collect secondary outcomes during hospital admission. These  
50  
51 outcomes include:

52  
53  
54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56  
57 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
58  
59 published or disclosed without prior written approval.

- 1
- 2
- 3 1. ICU and hospital delirium/coma-free days assessed twice daily until postoperative day 3.
- 4
- 5 Delirious patients will be assessed until postoperative day 5. In the event that delirium
- 6
- 7 does not resolve by postoperative day 5, assessments will continue until postoperative
- 8
- 9 day 7 or hospital discharge.
- 10
- 11 2. Severity of delirium scored using the CAM delirium severity scoring long form
- 12
- 13 3. Date of hospital discharge and length of hospital stay assessed by chart review
- 14
- 15
- 16 4. Inpatient mortality and major inpatient morbidity assessed by chart review
- 17

### 18 **Secondary outcomes (post-discharge)**

19 Blinded trial staff will collect secondary outcomes via telephone interviews and/or online  
20 questionnaires at 30-days, 90-days, and 180-days post procedure. These outcomes include:  
21

- 22 1. Cognitive function using the abbreviated Montreal Cognitive Assessment
- 23
- 24 2. Physical function with the PROMIS SF v1.2 - Physical Function 8b
- 25
- 26 3. General health with the PROMIS SF v1.1 - Global
- 27
- 28 4. Pain with the PROMIS SF v1.0- Pain Interference 8a
- 29
- 30 5. Applied cognition with the PROMIS v1.0 - Applied Cognition Abilities SF 8a
- 31
- 32 6. Sleep quality with the PROMIS v1.0 - Sleep Disturbance 4A
- 33
- 34 7. Mortality assessed by chart review, and/or elicited from family member during follow-up  
35 calls  
36
- 37
- 38
- 39
- 40

### 41 **Sample size planning**

42 The primary objective of this trial is to detect a difference in the incidence of delirium  
43 between the dexmedetomidine-induced sleep and normal care groups. Assuming a delirium  
44 event rate of 15%, a type I error of 0.05, and power of 0.90, an n = 184 patients per group will  
45 enable us to detect an absolute difference 10% (i.e., 15% versus 5%). With respect to  
46 decreased morbidity and healthcare costs, this change represents a clinically meaningful  
47 difference. Therefore, we will recruit 370 patients.  
48

49 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
50 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
51 published or disclosed without prior written approval.  
52

## Recruitment

This study will be performed at the Massachusetts General Hospital in Boston, MA. Subjects will be recruited through the cardiac surgery preoperative clinic and all enrolled patients will provide written informed consent. Informed consent for this protocol will follow a two-part process. First, a verbal consent will be obtained at the pre-operative visit prior to administering pre-operative baseline questionnaires. During this visit, the trial protocol will be explained to potential participants. In addition, a flyer detailing an overview of the trial protocol, as well as a copy of the formal consent form, will be given to potential trial participants to take home. A study physician will obtain final, written consent on the day of surgery (typically within 14 days of the pre-operative visit). After written consent is obtained, the trial team will allocate a trial identification number to the subject based on the trial stratification schema. A clinical trial pharmacist will perform central allocation into study arms according to the randomization key that is associated with each trial identification number.

## Allocation

Eligible patients who provide written informed consent will be randomized to receive either dexmedetomidine or placebo with a 1:1 allocation as per a computer-generated randomization schedule generated by an independent statistician, and stratified by cardiac surgery type (i.e. valvular repair versus non-valvular repair) using permuted blocks of random sizes. The block sizes will not be disclosed until the primary endpoint is analyzed to ensure concealment. Allocation concealment is further ensured by the fact that dexmedetomidine and placebo cannot be distinguished on the basis of appearance. The randomization key that is associated with each participant trial identification number will remain with the clinical trial pharmacist (AD) for the duration of the study. Thus, the clinical trial pharmacist will conduct randomization throughout the study in order to keep the data management team and the statistician blind. All trial medications will be labeled as “dexmedetomidine or placebo,” to

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.



1  
2  
3 preserve the integrity of randomization assignments. Thus, randomization into any study arm  
4 will be conducted without any influence of the study investigators, biostatisticians, and outcome  
5 assessors. The CSICU nurse taking care of the patient will administer the trial medication. If  
6 other medications are indicated for the treatment of delirium, the treating physician will prescribe  
7 this as part of standard clinical care.  
8  
9  
10  
11  
12

### 13 **Blinding**

14  
15 Assessors who are blind to treatment allocation will conduct all primary and secondary outcome  
16 assessments. To maintain the overall quality and legitimacy of the clinical trial, code breaks will  
17 occur only in exceptional circumstances when knowledge of the actual treatment is deemed  
18 essential by the treating physicians for further management of the patient. The treating  
19 physician will be directed to the clinical trial pharmacist to obtain the actual treatment code. The  
20 study investigators will maintain blindness and the treatment allocation. Additionally, the treating  
21 physician will be directed to abstain from written or verbal disclosure of the code. The principal  
22 investigator (PI) will report all code breaks to the DSMB.  
23  
24  
25  
26  
27  
28  
29  
30  
31

### 32 **Criteria for patient discontinuation**

33  
34 Patients may be discontinued from trial treatment and assessments for several reasons.  
35 These include: voluntary discontinuation by the patient, safety reasons (i.e. active hemorrhage)  
36 as judged by the clinical and/or trial physicians, failure to maintain study eligibility during the  
37 hospital stay or non-compliance with the protocol as judged by the trial physician.  
38  
39  
40  
41  
42

### 43 **Data analysis**

44 All trial outcomes will be evaluated using a modified intention-to-treat analysis plan.  
45 Hypothesis tests will be performed using a two-sided significance level (type I error) of  $\alpha=0.05$ .  
46 Sensitivity analyses using the actual treatment received will also be performed and compared  
47 with the intention-to-treat analysis results. Additional sensitivity analyses will be performed to  
48 assess the potential impact of missing data due to follow-up losses. The primary outcome will  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59



1  
2  
3 be evaluated using logistic regression examining the presence or absence of delirium  
4 conditional on randomized group assignment. Any randomization imbalances, or other potential  
5 treatment effect modifiers will be further examined as covariates in sensitivity analyses.  
6  
7 Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will  
8 use Pearson  $\chi^2$  tests to compare categorical variables between the 2 trial groups and  
9 independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event  
10 analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal  
11 care on mortality, and CSICU and hospital lengths of stay. Kaplan-Meier survival curves will be  
12 used for graphical presentation of these time-to-event analyses, and log-rank statistics will be  
13 used to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients  
14 will be censored at the time of last contact alive. Censoring for CSICU or hospital discharge  
15 readiness analyses will occur at time of death or trial withdrawal. Because missing data rarely  
16 occur entirely at random, we will assess the associations between patient characteristics with  
17 respect to missing data. If patients with at least one missing outcome value are different from  
18 those with complete outcomes data, we will use multiple imputation to assign values to missing  
19 data risk factors and outcomes in regression modeling.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35

### 36 37 **Heterogeneity of treatment effects**

38  
39 Subgroup comparisons will be conducted for heterogeneity of treatment-covariate  
40 interactions if the sample sizes and numbers of events within these subgroups are sufficient for  
41 analysis. If there is a treatment difference together with evidence of heterogeneity, relevant  
42 covariates and interaction terms will be added to the relevant regression models for formal  
43 significance testing. For the primary outcome, we plan for analyses of treatment effects within  
44 pre-specified subgroups potentially defined by:  
45  
46  
47  
48  
49  
50

#### 51 52 1. Surgery type

53  
54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

2. Length of cardiopulmonary bypass
3. Presence of significant cardiac dysfunction (ejection fraction less than 35%)
4. Sedative administration in the ICU
5. Opioid administration in the ICU
6. Pain scores
7. Baseline cognitive status
8. Organ failure
9. Postoperative cerebrovascular disease
10. APACHE/EUROscore

### **Interim analyses**

Interim efficacy data will be provided to the Data Safety Monitoring Board (DSMB) during yearly meetings to permit benefit-to-risk assessments. An independent statistician that is unblinded to the treatment allocation will perform the interim-analysis. The statistician will report to the DSMB in a closed session. Thus, the DSMB will have unblinded access to all data to inform recommendations. If at any time during the course of the study the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

### **Data management**

All data collected for the MINDDS trial will be entered into the Massachusetts General Hospital Research Electronic Data Capture (REDCap) application.<sup>66</sup> Data entered into the database will be retrievable for viewing through the data entry applications. Data integrity will be enforced through referential data rules, valid values, range checks, and consistency checks against data already stored in the database. Programs designed to detect missing data or specific errors in the data will be implemented to detect additional errors. These errors will be

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

1  
2  
3 summarized along with detailed descriptions for each specific problem in monthly Data Query  
4 Reports, which will be sent to the PI. The PI will respond by checking the original forms for  
5 inconsistency, checking other sources to determine the correction, modifying the original forms  
6 as necessary, and entering a response to the query. Data access will be restricted via password  
7 protection to only those individuals who are authorized to work on the trial. Specific privilege  
8 assignments within the database will also be employed to limit the types of data that authorized  
9 users may access to the minimum required by their role in the trial. Electronic audit trails will be  
10 used to capture and record changes to database contents automatically. Original study forms  
11 will also be kept in files. Participant files will be stored in numerical order in a secure and  
12 accessible place and manner. These files will be maintained in storage for a period of at least 5  
13 years after study completion. Members of the adjudication committee will request a subset of  
14 these study forms later for quality control.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29

### 30 **Site training**

31  
32 Trial team members have undergone a rigorous CAM training program led by a  
33 neuropsychologist and member of the team that created the Long-CAM.<sup>65</sup> The CAM is the most  
34 widely used delirium assessment tool in the research setting, with a high sensitivity and  
35 specificity when compared with formal psychiatric diagnosis.<sup>64 65</sup> The 3D-CAM is a three-minute  
36 assessment tool for delirium, which has good agreement with the CAM.<sup>67</sup> Those who attended  
37 this initial training will oversee the training of other team members. All trainees must  
38 demonstrate competence at conducting the structured interviews and in correctly scoring  
39 subjects. Trainees must first conduct at least two satisfactory CAM assessments in subjects not  
40 enrolled in the MINDDS trial in the presence of a trained team member. To establish  
41 competency in scoring the CAM, trainees will observe CAM interviews conducted by trained  
42 team members and will score the CAM independently. The trainee must agree with the trainer  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

1  
2  
3 on the presence or absence of all cognitive features assessed by the CAM on a minimum of six  
4 interviews. After meeting the stipulations of training, the newly trained team member will  
5 conduct their first interview of a patient enrolled into the MINDDS trial in the presence of a  
6 previously trained team member. Independent of the training process, all MINDDS team  
7 members who are participating in CAM assessments must view and rate videos of CAM  
8 interviews of actors depicting delirious and non-delirious patients.  
9  
10  
11  
12  
13  
14

### 15 16 **Data and safety monitoring**

17 All unexpected adverse events that are related to the trial treatment will be recorded in  
18 the trial database and reported as required to the Partners Healthcare IRB. A data and safety  
19 monitoring board (DSMB) will also oversee the MINDDS trial. The DSMB will provide  
20 independent oversight of the MINDDS, and will review general conduct of the trial and trial data  
21 for participant safety. The DSMB is comprised of independent, multidisciplinary experts who will  
22 make recommendations regarding the continuation, modification, or termination of the trial for  
23 harm from intervention. The members will have the requisite expertise to examine accumulating  
24 data, to protect the integrity of the clinical experiments to which the patients have consented to  
25 participate, and to assure the regulatory bodies, the public and the National Institutes of Health  
26 that conflicts of interest do not compromise either patient safety or trial integrity. The DSMB will  
27 convene before trial initiation and annually to review safety events. Recommendations from the  
28 DSMB for protocol modifications or revisions will be communicated through a representative of  
29 the National Institutes on Aging to the PI.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

45 The study operations committee will determine relatedness of an event to the study drug  
46 based on a temporal relationship to the study drug administration, whether the event is  
47 unexpected given the clinical course, previous medical conditions, and concomitant  
48 medications. Adverse events will also be communicated to members of the study steering  
49 committee for additional review. Expedited review will occur for all events meeting the FDA  
50  
51  
52  
53

54  
55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58  
59

1  
2  
3 definition of SAEs – i.e., any fatal event, immediately life-threatening event, permanently or  
4 substantially disabling event, or event requiring or prolonging inpatient hospitalization. This also  
5 includes any event that a study investigator or the DSMB judges to impose a significant hazard,  
6  
7 contraindication, side effect, or precaution. For purposes of this study, all SAEs will require  
8 reporting to the DSMB. All relevant information will be reported to the DSMB for each SAE,  
9 including information about the event and its outcome, dosing history of all study drugs,  
10 concomitant medications, the subject's medical history and current conditions, and all relevant  
11 laboratory data. Notification by e-mail of all related study forms shall be made to the DSMB  
12 within 2 days of the occurrence of any SAE. Information will be reviewed and a determination  
13 made of whether there was any possible relevance to the study drug. Additional reporting to the  
14 IRB will be done within 24 hours of the SAE. All patients that experience a SAE will be censored  
15 from the study at SAE occurrence.

### 28 **Data Monitoring and Quality Assurance**

29  
30 Reflective of the state of the art in clinical trials, the MINDDS trial will employ a web-  
31 based portal for data quality and completeness. The portal will display in real time the following  
32 variables for all patients: sex, race, adverse events, study related data etc.

### 36 **Trial risks**

37  
38 The risk of a breach of confidentiality is small and all possible efforts have been taken to  
39 ensure the security of trial data and minimize the risks of accidental disclosure of identifiable  
40 data elements. The risks associated with dexmedetomidine are related to drug induced  
41 reduction in sympathetic activity, resulting in hypotension and bradycardia. However,  
42 cardiovascular parameters are continuously monitored in the CSICU, ensuring that appropriate  
43 medical intervention can be instituted in a timely fashion for clinically significant hypotensive or  
44 bradycardic episodes. Thus, the risk of clinically significant hypotension or bradycardia in our  
45 patient study population is small.

46  
47 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
48 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
49 published or disclosed without prior written approval.

## Ethics and dissemination

The Partners Health Care IRB has approved the trial. The trial steering committee will be responsible for all major decisions regarding changes to the protocol. The committee will communicate these changes to the IRB and the DSMB. Electronic data and demographic information will be accessed only as necessary for completion of trial follow-up tasks. The PI has will have access to all data. The primary papers emanating from MINDDS will present primary and secondary outcome. Secondary analyses will also be conducted to construct predictive models for delirium occurrence and resource utilization. Mechanistic manuscripts on the pathophysiology of delirium from sub-studies (i.e. electroencephalogram dynamics, biomarker discovery, brain imaging) will also be published. Dissemination plans include presentations at local, national and international scientific conferences. Every effort will be made to publish results of the MINDDS trial in a peer-reviewed journal. Dissemination of results to trial participants and their family members will be available upon request. Updates and results of the trial will be available to the public at [clinicaltrials.gov](http://clinicaltrials.gov).

In summary, the MINDDS trial will evaluate a new preemptive therapeutic sleep strategy for the prevention of delirium, and may enable new insights into the pathophysiology of delirium.

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.

## References

1. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *Journal of the American Geriatrics Society* 2010;58(4):643-9. doi: 10.1111/j.1532-5415.2010.02762.x [published Online First: 2010/03/30]
2. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. Washington, D.C.: American Psychiatric Association 2013.
3. Hamilton GM, Wheeler K, Di Michele J, et al. A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality. *Anesthesiology* 2017;127(1):78-88. doi: 10.1097/ALN.0000000000001660
4. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2013;21(12):1190-222. doi: 10.1016/j.jagp.2013.09.005 [published Online First: 2013/11/12]
5. Shearer WT, Reuben JM, Mullington JM, et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *The Journal of allergy and clinical immunology* 2001;107(1):165-70. doi: 10.1067/mai.2001.112270
6. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* 2007;30(9):1145-52.
7. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *The Journal of clinical endocrinology and metabolism* 2004;89(5):2119-26. doi: 10.1210/jc.2003-031562
8. Johns MW, Large AA, Masterton JP, et al. Sleep and delirium after open heart surgery. *The British journal of surgery* 1974;61(5):377-81. [published Online First: 1974/05/01]
9. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Critical care medicine* 2002;30(3):536-40. [published Online First: 2002/05/07]
10. Munster BC, Aronica E, Zwinderman AH, et al. Neuroinflammation in delirium: a postmortem case-control study. *Rejuvenation research* 2011;14(6):615-22. doi: 10.1089/rej.2011.1185
11. Siami S, Annane D, Sharshar T. The encephalopathy in sepsis. *Critical care clinics* 2008;24(1):67-82, viii. doi: 10.1016/j.ccc.2007.10.001
12. O'Keeffe ST, Ni Chonchubhair A. Postoperative delirium in the elderly. *British journal of anaesthesia* 1994;73(5):673-87.
13. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. *Injury* 2007;38(12):1336-45. doi: 10.1016/j.injury.2007.10.003
14. Shimaoka M, Park EJ. Advances in understanding sepsis. *European journal of anaesthesiology Supplement* 2008;42:146-53. doi: 10.1017/S0265021507003389
15. Weichhart T, Haidinger M, Horl WH, et al. Current concepts of molecular defence mechanisms operative during urinary tract infection. *European journal of clinical investigation* 2008;38 Suppl 2:29-38. doi: 10.1111/j.1365-2362.2008.02006.x
16. Bjornsson GL, Thorsteinsson L, Gudmundsson KO, et al. Inflammatory cytokines in relation to adrenal response following total hip replacement. *Scandinavian journal of immunology* 2007;65(1):99-105. doi: 10.1111/j.1365-3083.2006.01872.x
17. Kraggsbjerg P, Holmberg H, Vikersfors T. Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. *The European journal of surgery = Acta chirurgica* 1995;161(1):17-22.

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.



18. Keck M, Herndon DH, Kamolz LP, et al. Pathophysiology of burns. *Wiener medizinische Wochenschrift* 2009;159(13-14):327-36. doi: 10.1007/s10354-009-0651-2
19. Marx N, Neumann FJ, Ott I, et al. Induction of cytokine expression in leukocytes in acute myocardial infarction. *Journal of the American College of Cardiology* 1997;30(1):165-70.
20. Asimakopoulos G. Mechanisms of the systemic inflammatory response. *Perfusion* 1999;14(4):269-77.
21. Sun Y, Tawara I, Toubai T, et al. Pathophysiology of acute graft-versus-host disease: recent advances. *Translational research : the journal of laboratory and clinical medicine* 2007;150(4):197-214. doi: 10.1016/j.trsl.2007.06.003
22. Stingham AE, Goncalves SM, Martines EG, et al. Increased plasma and endothelial cell expression of chemokines and adhesion molecules in chronic kidney disease. *Nephron Clinical practice* 2009;111(2):c117-26. doi: 10.1159/000191205
23. Shawcross DL, Shabbir SS, Taylor NJ, et al. Ammonia and the neutrophil in the pathogenesis of hepatic encephalopathy in cirrhosis. *Hepatology* 2010;51(3):1062-9. doi: 10.1002/hep.23367
24. van Munster BC, Korevaar JC, Zwinderman AH, et al. Time-course of cytokines during delirium in elderly patients with hip fractures. *Journal of the American Geriatrics Society* 2008;56(9):1704-9. doi: 10.1111/j.1532-5415.2008.01851.x
25. Culley DJ, Snayd M, Baxter MG, et al. Systemic inflammation impairs attention and cognitive flexibility but not associative learning in aged rats: possible implications for delirium. *Frontiers in aging neuroscience* 2014;6:107. doi: 10.3389/fnagi.2014.00107
26. Cerejeira J, Firmino H, Vaz-Serra A, et al. The neuroinflammatory hypothesis of delirium. *Acta neuropathologica* 2010;119(6):737-54. doi: 10.1007/s00401-010-0674-1 [published Online First: 2010/03/24]
27. Norden DM, Godbout JP. Review: microglia of the aged brain: primed to be activated and resistant to regulation. *Neuropathology and applied neurobiology* 2013;39(1):19-34. doi: 10.1111/j.1365-2990.2012.01306.x [published Online First: 2012/10/09]
28. Cunningham C. Systemic inflammation and delirium: important co-factors in the progression of dementia. *Biochemical Society transactions* 2011;39(4):945-53. doi: 10.1042/BST0390945 [published Online First: 2011/07/27]
29. Rosenberg-Adamsen S, Kehlet H, Dodds C, et al. Postoperative sleep disturbances: mechanisms and clinical implications. *British journal of anaesthesia* 1996;76(4):552-9. [published Online First: 1996/04/01]
30. Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *British medical journal* 1985;290(6474):1029-32. [published Online First: 1985/04/06]
31. Ellis BW, Dudley HA. Some aspects of sleep research in surgical stress. *Journal of psychosomatic research* 1976;20(4):303-8. [published Online First: 1976/01/01]
32. Kavey NB, Ahshuler KZ. Sleep in herniorrhaphy patients. *American journal of surgery* 1979;138(5):683-7. [published Online First: 1979/11/01]
33. Lehmkuhl P, Prass D, Pichlmayr I. General anesthesia and postnarcotic sleep disorders. *Neuropsychobiology* 1987;18(1):37-42. doi: 118390 [published Online First: 1987/01/01]
34. Akeju O, Brown EN. Neural oscillations demonstrate that general anesthesia and sedative states are neurophysiologically distinct from sleep. *Curr Opin Neurobiol* 2017;44:178-85. doi: 10.1016/j.conb.2017.04.011
35. Akeju O, Hobbs LE, Gao L, et al. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: A pilot study. *Clin Neurophysiol* 2017;129(1):69-78. doi: 10.1016/j.clinph.2017.10.005

CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval.



- 1
- 2
- 3 36. van Lier H, Drinkenburg WH, van Eeten YJ, et al. Effects of diazepam and zolpidem on EEG
- 4 beta frequencies are behavior-specific in rats. *Neuropharmacology* 2004;47(2):163-74.
- 5 doi: 10.1016/j.neuropharm.2004.03.017 [published Online First: 2004/06/30]
- 6 37. Feinberg I, Maloney T, Campbell IG. Effects of hypnotics on the sleep EEG of healthy young
- 7 adults: new data and psychopharmacologic implications. *Journal of psychiatric research*
- 8 2000;34(6):423-38. [published Online First: 2001/02/13]
- 9 38. Patat A, Trocherie S, Thebault JJ, et al. EEG profile of intravenous zolpidem in healthy
- 10 volunteers. *Psychopharmacology* 1994;114(1):138-46. [published Online First:
- 11 1994/02/01]
- 12 39. Akeju O, Pavone KJ, Westover MB, et al. A comparison of propofol- and dexmedetomidine-
- 13 induced electroencephalogram dynamics using spectral and coherence analysis.
- 14 *Anesthesiology* 2014;121(5):978-89. doi: 10.1097/ALN.0000000000000419 [published
- 15 Online First: 2014/09/05]
- 16 40. Akeju O, Westover MB, Pavone KJ, et al. Effects of sevoflurane and propofol on frontal
- 17 electroencephalogram power and coherence. *Anesthesiology* 2014;121(5):990-8. doi:
- 18 10.1097/ALN.0000000000000436 [published Online First: 2014/09/19]
- 19 41. Purdon PL, Pierce ET, Mukamel EA, et al. Electroencephalogram signatures of loss and
- 20 recovery of consciousness from propofol. *Proceedings of the National Academy of*
- 21 *Sciences of the United States of America* 2013;110(12):E1142-51. doi:
- 22 10.1073/pnas.1221180110 [published Online First: 2013/03/15]
- 23 42. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society
- 24 updated Beers Criteria for potentially inappropriate medication use in older adults.
- 25 *Journal of the American Geriatrics Society* 2012;60(4):616-31. doi: 10.1111/j.1532-
- 26 5415.2012.03923.x
- 27 43. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2
- 28 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology* 1992;76(6):948-52.
- 29 [published Online First: 1992/06/01]
- 30 44. Lu J, Nelson LE, Franks N, et al. Role of endogenous sleep-wake and analgesic systems in
- 31 anesthesia. *The Journal of comparative neurology* 2008;508(4):648-62. doi:
- 32 10.1002/cne.21685 [published Online First: 2008/04/03]
- 33 45. Mizobe T, Maghsoudi K, Sitwala K, et al. Antisense technology reveals the alpha2A
- 34 adrenoceptor to be the subtype mediating the hypnotic response to the highly selective
- 35 agonist, dexmedetomidine, in the locus coeruleus of the rat. *The Journal of clinical*
- 36 *investigation* 1996;98(5):1076-80. doi: 10.1172/JCI118887 [published Online First:
- 37 1996/09/01]
- 38 46. Nacif-Coelho C, Correa-Sales C, Chang LL, et al. Perturbation of ion channel conductance
- 39 alters the hypnotic response to the alpha 2-adrenergic agonist dexmedetomidine in the
- 40 locus coeruleus of the rat. *Anesthesiology* 1994;81(6):1527-34. [published Online First:
- 41 1994/12/01]
- 42 47. Nelson LE, Lu J, Guo T, et al. The alpha2-adrenoceptor agonist dexmedetomidine
- 43 converges on an endogenous sleep-promoting pathway to exert its sedative effects.
- 44 *Anesthesiology* 2003;98(2):428-36. [published Online First: 2003/01/29]
- 45 48. Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity
- 46 during dexmedetomidine sedation and physiological sleep. *Acta anaesthesiologica*
- 47 *Scandinavica* 2008;52(2):289-94. doi: 10.1111/j.1399-6576.2007.01537.x [published
- 48 Online First: 2007/11/17]
- 49 49. Alexopoulou C, Kondili E, Diamantaki E, et al. Effects of dexmedetomidine on sleep quality
- 50 in critically ill patients: a pilot study. *Anesthesiology* 2014;121(4):801-7. doi:
- 51 10.1097/ALN.0000000000000361 [published Online First: 2014/07/06]

52 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
53 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
54 published or disclosed without prior written approval.

- 1
- 2
- 3
- 4 50. Oto J, Yamamoto K, Koike S, et al. Sleep quality of mechanically ventilated patients sedated  
5 with dexmedetomidine. *Intensive care medicine* 2012;38(12):1982-9. doi:  
6 10.1007/s00134-012-2685-y [published Online First: 2012/09/11]
- 7 51. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of  
8 critically ill patients: a randomized trial. *Jama* 2009;301(5):489-99. doi:  
9 10.1001/jama.2009.56 [published Online First: 2009/02/04]
- 10 52. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs  
11 lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS  
12 randomized controlled trial. *Jama* 2007;298(22):2644-53. doi: 10.1001/jama.298.22.2644  
13 [published Online First: 2007/12/13]
- 14 53. Reade MC, Eastwood GM, Bellomo R, et al. Effect of Dexmedetomidine Added to Standard  
15 Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical  
16 Trial. *Jama* 2016;316(7):773-4. doi: 10.1001/jama.2016.2707 [published Online First:  
17 2016/03/16]
- 18 54. Maldonado JR, Wysong A, van der Starre PJ, et al. Dexmedetomidine and the reduction of  
19 postoperative delirium after cardiac surgery. *Psychosomatics* 2009;50(3):206-17. doi:  
20 10.1176/appi.psy.50.3.206 [published Online First: 2009/07/02]
- 21 55. Wafford KA, Ebert B. Emerging anti-insomnia drugs: tackling sleeplessness and the quality  
22 of wake time. *Nature reviews Drug discovery* 2008;7(6):530-40. doi: 10.1038/nrd2464  
23 [published Online First: 2008/05/31]
- 24 56. Huber R, Ghilardi MF, Massimini M, et al. Local sleep and learning. *Nature*  
25 2004;430(6995):78-81. doi: 10.1038/nature02663 [published Online First: 2004/06/09]
- 26 57. Huber R, Ghilardi MF, Massimini M, et al. Arm immobilization causes cortical plastic  
27 changes and locally decreases sleep slow wave activity. *Nature neuroscience*  
28 2006;9(9):1169-76. doi: 10.1038/nn1758 [published Online First: 2006/08/29]
- 29 58. Huber R, Tononi G, Cirelli C. Exploratory behavior, cortical BDNF expression, and sleep  
30 homeostasis. *Sleep* 2007;30(2):129-39. [published Online First: 2007/03/01]
- 31 59. Rasch B, Buchel C, Gais S, et al. Odor cues during slow-wave sleep prompt declarative  
32 memory consolidation. *Science* 2007;315(5817):1426-9. doi: 10.1126/science.1138581  
33 [published Online First: 2007/03/10]
- 34 60. Backhaus J, Junghanns K, Born J, et al. Impaired declarative memory consolidation during  
35 sleep in patients with primary insomnia: Influence of sleep architecture and nocturnal  
36 cortisol release. *Biological psychiatry* 2006;60(12):1324-30. doi:  
37 10.1016/j.biopsych.2006.03.051 [published Online First: 2006/08/01]
- 38 61. Molle M, Marshall L, Gais S, et al. Learning increases human electroencephalographic  
39 coherence during subsequent slow sleep oscillations. *Proceedings of the National*  
40 *Academy of Sciences of the United States of America* 2004;101(38):13963-8. doi:  
41 10.1073/pnas.0402820101 [published Online First: 2004/09/10]
- 42 62. Prehn-Kristensen A, Munz M, Goder R, et al. Transcranial oscillatory direct current  
43 stimulation during sleep improves declarative memory consolidation in children with  
44 attention-deficit/hyperactivity disorder to a level comparable to healthy controls. *Brain*  
45 *stimulation* 2014;7(6):793-9. doi: 10.1016/j.brs.2014.07.036 [published Online First:  
46 2014/08/26]
- 47 63. Marshall L, Molle M, Hallschmid M, et al. Transcranial direct current stimulation during sleep  
48 improves declarative memory. *The Journal of neuroscience : the official journal of the*  
49 *Society for Neuroscience* 2004;24(44):9985-92. doi: 10.1523/JNEUROSCI.2725-  
50 04.2004 [published Online First: 2004/11/05]
- 51
- 52
- 53
- 54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.

- 1  
2  
3 64. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment  
4 method. A new method for detection of delirium. *Annals of internal medicine*  
5 1990;113(12):941-8. [published Online First: 1990/12/15]  
6 65. Ramaswamy R, Dix EF, Drew JE, et al. Beyond grand rounds: a comprehensive and  
7 sequential intervention to improve identification of delirium. *The Gerontologist*  
8 2011;51(1):122-31. doi: 10.1093/geront/gnq075  
9 66. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a  
10 metadata-driven methodology and workflow process for providing translational research  
11 informatics support. *Journal of biomedical informatics* 2009;42(2):377-81. doi:  
12 10.1016/j.jbi.2008.08.010 [published Online First: 2008/10/22]  
13 67. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-  
14 minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test  
15 study. *Annals of internal medicine* 2014;161(8):554-61. doi: 10.7326/M14-0865  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 CONFIDENTIAL: This document is the intellectual property the MINDDS research group. Acceptance of this  
56 document constitutes the agreement by the recipient that no unpublished information contained herein will be  
57 published or disclosed without prior written approval.  
58



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1, 6
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1, 6
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 1-6 and 10, 11, 35
	5b	Name and contact information for the trial sponsor	Page 6
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Pages 10-12, 35

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47**Introduction**

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pages 15-17
	6b	Explanation for choice of comparators	Pages 16-17?
Objectives	7	Specific objectives or hypotheses	Page 17
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 17

**Methods: Participants, interventions, and outcomes**

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 19, 22
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 19
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 18, 20, 23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 20, 22
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 19-20, 23, 28
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 20-21
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Pages 19-22

1  
2  
3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including Page 13,17, 21  
4 clinical and statistical assumptions supporting any sample size calculations

5  
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size Page 22  
7

8 **Methods: Assignment of interventions (for controlled trials)**  
9

10 Allocation:

11  
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any Pages 19, 22-24  
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
15 or assign interventions  
16

17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, Page 22, 23  
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  
19  
20

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to Page 22  
22 interventions  
23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome Pages 22-23  
25 assessors, data analysts), and how  
26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's Page 23, 25  
28 allocated intervention during the trial  
29  
30

31 **Methods: Data collection, management, and analysis**  
32

33 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related Pages 19-22, 25-  
34 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of 26  
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
36 Reference to where data collection forms can be found, if not in the protocol  
37

38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be Pages 20-21  
39 collected for participants who discontinue or deviate from intervention protocols  
40  
41  
42  
43  
44

1				
2				
3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 25-26, 28
4				
5				
6				
7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 23-24
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pages 24-25
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pages 23-24
13				
14				
15	<b>Methods: Monitoring</b>			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Pages 27-28
18				
19				
20				
21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 25
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Pages 27-28
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Pages 27-28
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 29
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Pages 27-29
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				





1				
2				
3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 22
4				
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 22
7				
8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17, 19, 21, 26, 28
9				
10				
11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10
12				
13				
14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 29
15				
16				
17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page 28
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 29
21				
22				
23				
24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	Page 10, 35
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 29
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
35				
36				

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
 40

# BMJ Open

## Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020316.R2
Article Type:	Protocol
Date Submitted by the Author:	22-Feb-2018
Complete List of Authors:	<p>Shelton, Kenneth; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Qu, Jason; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Bilotta, Federico; University of Rome "Sapienza", Anesthesiology</p> <p>Brown, Emery; Massachusetts Institute of Technology Institute for Medical Engineering and Science; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Cudemus, Gaston; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>D'Alessandro, David; Massachusetts General Hospital, Department of Surgery, Division of Cardiac Surgery</p> <p>Deng, Hao; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>DiBiasio, Alan; Massachusetts General Hospital, Department of Pharmacy</p> <p>Gitlin, Jacob; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Hahm, Eunice; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Hobbs, Lauren; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Houle, Timothy T. ; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Ibala, Reine; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Loggia, Marco; Massachusetts General Hospital, Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology</p> <p>Pavone, Kara; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p> <p>Shaefi, Shahzad; Beth Israel Deaconess Medical Center, Department of Anesthesia and Critical Care</p> <p>Tolis, George; Massachusetts General Hospital, Department of Surgery, Division of Cardiac Surgery</p> <p>Westover, Brandon; Massachusetts General Hospital, Department of Neurology</p> <p>Akeju, Oluwaseun; Massachusetts General Hospital, Department of Anesthesiology, Critical Care, and Pain Medicine</p>
<b>Primary Subject	Intensive care

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Heading</b> :	
Secondary Subject Heading:	Anaesthesia, Cardiovascular medicine, Neurology
Keywords:	Delirium, Biomimetic sleep, Dexmedetomidine, Cardiac surgery < SURGERY, Patient reported outcomes

SCHOLARONE™  
Manuscripts

For peer review only

1  
2  
3 **Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep**  
4 **(MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial**  
5  
6  
7

8 KT Shelton<sup>1</sup>, J Qu<sup>1</sup>, F Bilotta<sup>2</sup>, EN Brown<sup>1,3</sup>, G Cudemus<sup>1</sup>, DA D'Alessandro<sup>4</sup>, H Deng<sup>1</sup>, A  
9 DiBiasio<sup>5</sup>, J Gitlin<sup>1</sup>, EY Hahm<sup>1</sup>, LE Hobbs<sup>1</sup>, TT Houle<sup>1</sup>, R Ibalá<sup>1</sup>, M Loggia<sup>6</sup>, KJ Pavone<sup>1</sup>, S  
10 Shaefi<sup>7</sup>, G Tolis<sup>4</sup>, MB Westover, O Akeju\*<sup>1</sup>  
11

12 **Affiliations:**

13 <sup>1</sup> Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General  
14 Hospital, Boston MA, 02114

15 <sup>2</sup> Department of Anaesthesia and Critical Care Medicine, "Sapienza" University Rome

16 <sup>3</sup> Institute for Medical Engineering and Sciences, Massachusetts Institute of Technology,  
17 Cambridge MA, 02139

18 <sup>4</sup> Department of Surgery, Division of Cardiac Surgery, Massachusetts General Hospital, Boston  
19 MA, 02114

20 <sup>5</sup> Department of Pharmacy, Massachusetts General Hospital, Boston MA, 02114

21 <sup>6</sup> Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology,  
22 Massachusetts General Hospital, Boston MA, 02114

23 <sup>7</sup> Department of Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, Boston  
24 MA, 02215

25 <sup>8</sup> Department of Neurology, Massachusetts General Hospital, Boston MA, 02114  
26  
27  
28  
29

30 \*To whom correspondence should be addressed

31 Oluwaseun Johnson-Akeju

32 Massachusetts General Hospital

33 Department of Anesthesia, Critical Care and Pain Medicine

34 55 Fruit St

35 Boston, MA 02114

36 USA

37 oluwaseun.akeju@mgh.harvard.edu  
38  
39  
40  
41  
42

43 **Version:** February 20, 2018

44 **Amendment 2:**

45 NCT02856594

46  
47 Funding for the MINDDS trial is through a grant awarded by the National Institutes on Aging  
48 (R01 AG053582).  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **Authors' contributions:** Authorship for this trial will be given to key personnel involved in trial  
4 design, recruitment, data collection, and data analysis. There are no publication restrictions and  
5 no professional writers will be involved in the generation of the manuscript. KTS, JQ, GC, HD,  
6 JG, EYH, LEH, TTH, RI, KJP, and OA were responsible for conceptualizing trial design. JQ  
7 managed patient safety protocol. EYH, JG RI, and LH were responsible for recruitment,  
8 enrolment, and data collection. KTS, JQ, FB, ENB, GC, DAD, HD, AD, JG EYH, LEH, TTH, RI,  
9 ML, KJP, SS, GT, MBW, and OA have critically revised the MINDDS protocol and approved the  
10 final version. All authors agree to be accountable for the accuracy and integrity of all aspects of  
11 the MINDDS trial.  
12  
13  
14  
15  
16  
17

18 **Conflict of interest statement:** OA and ENB have a provisional patent application describing  
19 the use of alpha-2 agonists for promoting N3 sleep. All other authors have no interests to  
20 declare.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Abstract

**Introduction:** Delirium, which is prevalent in post cardiac surgical patients, is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder. The pathophysiology of delirium remains poorly understood. However, basic science and clinical studies suggest that sleep disturbance may be a modifiable risk factor for the development of delirium. Dexmedetomidine is a  $\alpha_2$  adrenergic receptor agonist medication that patterns the activity of various arousal nuclei similar to sleep. A single nighttime loading dose of dexmedetomidine promotes non-rapid eye movement sleep stages N2 and N3 sleep. This trial hypothesizes dexmedetomidine-induced sleep as pre-emptive therapy for postoperative delirium.

**Methods and Analysis:** The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is a 370-patient block-randomized, placebo-controlled, double-blinded, single-site, parallel-arm superiority trial. Patients over 60 years old, undergoing cardiac surgery with planned cardiopulmonary bypass, will be randomized to receive a sleep inducing dose of dexmedetomidine or placebo. The primary outcome is the incidence of delirium on postoperative day 1, assessed with the Confusion Assessment Method by staff blinded to the treatment assignment. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 370 patients receive the study intervention on post-operative day 0. Secondary outcomes will be evaluated by in-person assessments and medical record review for in-hospital end points, and by telephone interview for 30-day, 90-day, and 180-day end points. All trial outcomes will be evaluated using an intention-to-treat analysis plan. Hypothesis testing will be performed using a two-sided significance level (type I error) of  $\alpha=0.05$ . Sensitivity analyses using the actual treatment received will be performed and compared with the intention-to-treat analysis results. Additional sensitivity analyses will assess the potential impact of missing data due to loss of follow-up.

1  
2  
3 **Ethics and dissemination:** The Partners Human Research Committee approved the MINDDS  
4  
5 trial. Recruitment began in March 2017. Dissemination plans include presentations at scientific  
6  
7 conferences, scientific publications, and popular media.  
8  
9

10 **Registration details:** NCT02856594.  
11

### 12 **Strengths and limitations**

- 14 • The treatment protocol is based on a plausible biological mechanism suggesting that  
15 biomimetic sleep may reduce the incidence of delirium.
- 16  
17 • The treatment protocol is straightforward and will allow the results to be generalized  
18  
19 to patients across a range of care settings.
- 20  
21 • Collection of patient-centered outcomes data, including measures of functional  
22  
23 independence, at up to 180-days will provide insight into the relationship between the  
24  
25 trial intervention and meaningful patient end points.
- 26  
27 • Risk factors and pathophysiological mechanisms of delirium will be explored in  
28  
29 separate sub-studies.
- 30  
31 • Delirium is a fluctuating disorder that may occasionally be missed despite rigorous  
32  
33 and validated assessment methods.  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## Introduction

Delirium, which is prevalent in post cardiac surgical patients,<sup>1</sup> is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition that is not explained by a preexisting neurocognitive disorder.<sup>2</sup> Although previously reported associations between delirium and increased mortality are debatable,<sup>3</sup> delirium remains a leading cause of preventable morbidity in hospitalized elderly patients.<sup>3,4</sup> The morbidity associated with delirium is estimated to result in increased healthcare costs of approximately \$16,000-\$64,000 per patient annually. Increasing age and pre-existing cognitive impairment are key predisposing factors for delirium. Despite its impact, there are no definitive pharmacological preventative strategies for delirium. However, basic science and clinical studies suggest that sleep disturbances may be a modifiable risk factor for the development of delirium.

Sleep is a natural occurring state of decreased arousal that is crucial for normal cardiovascular, immune and cognitive function. Sleep deprivation, which is associated with increased pro-inflammatory cytokine levels including interleukin-6,<sup>5-7</sup> precedes the onset of delirium in some patients.<sup>8,9</sup> A recent investigation linking brain activity of microglia, astrocytes, interleukin-6 and delirium in humans,<sup>10</sup> suggests a mechanistic link between sleep deprivation, brain inflammation, and delirium. Further, conditions associated with delirium are characterized by activation of the inflammatory cascade with acute release of inflammatory mediators.<sup>11-25</sup> Increasing age is a significant risk factor for the development of delirium. Notably, aging is associated with activated brain glia cell.<sup>4, 26</sup> Following a systemic challenge such as critical illness, these activated glia have been suggested to facilitate an exaggerated neuroinflammatory state that predisposes to delirium.<sup>4, 26-28</sup>

Sleep disturbance is a hallmark feature of the postoperative period,<sup>29-33</sup> and pharmacological induction of altered arousal states that are neurophysiologically indistinguishable from sleep, termed biomimetic sleep, may represent a preventative strategy for

1  
2  
3 the development of postoperative delirium.<sup>34 35</sup> However, commonly administered sedative  
4  
5 drugs, most of which modulate the  $\gamma$  amino butyric acid A (GABA<sub>A</sub>) receptor induce altered  
6  
7 arousal states that are neurophysiologically distinct from sleep.<sup>34 35</sup> This neurophysiological  
8  
9 distinction from sleep (i.e. frontal beta oscillations, frontal alpha oscillations, burst suppression,  
10  
11 isoelectricity)<sup>34-41</sup> may explain why current sedative medications that modulate GABA<sub>A</sub> receptors  
12  
13 are not delirium sparing. Rather, neural circuit dysfunction in sensory, memory encoding, and  
14  
15 cognitive processing circuits may in part explain why these medications are independent risk  
16  
17 factors for the development of delirium.<sup>34 42</sup>  
18  
19

20  
21 Dexmedetomidine is a  $\alpha$ 2a adrenergic receptor agonist medication that patterns the  
22  
23 activity of various arousal nuclei similar to sleep.<sup>43-47</sup> Neurophysiologically, a continuous infusion  
24  
25 of dexmedetomidine produces spindle and slow-delta oscillations.<sup>34 39 48</sup> This oscillatory dynamic  
26  
27 shares features with non-rapid eye movement (REM) sleep stage N2 sleep.<sup>34 39 49 50</sup> Consistent  
28  
29 with the hypothesis that the neurophysiological approximation of sleep may prevent delirium, the  
30  
31 dexmedetomidine-infusion N2 sleep stage (with absent non-REM stages N1, N3 and REM  
32  
33 sleep) has been associated with a reduced incidence of delirium in critically ill patients.<sup>51-54</sup>  
34  
35 Instead of a continuous drug infusion, we recently found that a single nighttime dose of  
36  
37 dexmedetomidine preserves normal sleep cycling.<sup>35</sup> This drug administration paradigm  
38  
39 promotes non-REM stage N3 sleep. Notably, N3 sleep is associated with improved cognition  
40  
41 and synaptic plasticity.<sup>55-63</sup>  
42  
43

44  
45 A neurophysiologically principled approach to pharmacologically promote sleep may  
46  
47 reduce significantly the incidence of delirium in hospitalized patients. The primary objective of  
48  
49 the MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep)  
50  
51 trial is to evaluate dexmedetomidine-induced sleep as a pharmacological preventative strategy  
52  
53 for delirium, and to characterize the impact of delirium prevention on patient-centered outcomes  
54  
55 such as functional recovery. In separate sub-studies, risk factors and pathophysiological  
56  
57  
58  
59  
60

1  
2  
3 mechanisms of delirium will be explored using: 1) unbiased serum metabolic, proteomic, and  
4 extracellular vesicular profiling; 2) power spectral analyses of intraoperative and CSICU  
5 electroencephalogram dynamics; and, 3) integrated positron emission tomography/magnetic  
6 resonance imaging of [<sup>11</sup>C] PBR28.  
7  
8  
9  
10

## 11 **Trial objectives**

12  
13  
14 Our primary hypothesis is that dexmedetomidine-induced sleep will result in a reduced  
15 incidence of delirium. Our intervention and control groups will be comprised of extubated  
16 cardiac surgical intensive care unit (CSICU) patients, because their relative homogeneity in  
17 terms of surgical procedures (i.e. cardiac surgery performed on cardiopulmonary bypass),  
18 anesthetic management, and systemic inflammatory response represents a unique opportunity  
19 to study the mechanisms underlying delirium, while limiting confounding factors that may  
20 otherwise be encountered in heterogeneous patients  
21  
22  
23  
24  
25  
26  
27  
28

## 29 **Methods and analysis**

### 30 **Trial design**

31  
32  
33 Study details including study team roster, organizational structure and responsibilities,  
34 are included in the supplementary file. We will enroll 370 patients over a period of three years  
35 into a randomized, controlled, double-blinded, single-site, parallel-arm superiority trial. Our  
36 primary outcome is the incidence of delirium on postoperative day 1 upon administration of the  
37 study intervention. To ensure that the study is appropriately powered for the primary outcome  
38 measure, patients will be recruited and randomized into the study until 370 patients receive the  
39 study intervention on post-operative day 0. Trial end points will be assessed via in-person  
40 interview (during hospitalization), medical record review, and telephone interview (after hospital  
41 discharge). The primary and secondary outcomes of delirium will be assessed via in-person  
42 interviews, which will be performed in the morning and afternoon with approximately 6 hours  
43 between interviews. All outcomes, including those obtained post discharge, will be assessed in  
44 a blinded fashion.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Eligibility criteria****Inclusion criteria**

1. Age  $\geq$  60
2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for  $\geq$  24 hours
3. Scheduled same day surgical admission

**Exclusion criteria**

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score  $>$  5
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit
9. Surgical procedure requiring total circulatory arrest

**Objective Drop Criteria**

1. Scheduled for a second surgical procedure during hospital stay
2. Postoperative intubation  $>$  12 hours

**Baseline assessment**

Patients will undergo a pre-randomization assessment that includes a brief medical record review, and evaluation the following:

- 1
- 2
- 3 1. Baseline cognitive function using the abbreviated Montreal Cognitive Assessment
- 4
- 5 2. Presence of delirium at the time of interview, as measured by the 3-min assessment for
- 6
- 7 Confusion Assessment Method-defined delirium (3D-CAM)
- 8
- 9 3. Physical function with the PROMIS SF v1.2 -Physical function 8b
- 10
- 11 4. General health with the PROMIS SF v1.1- Global
- 12
- 13 5. Pain with the PROMIS SF v1.0- Pain Interference 8a
- 14
- 15 6. Applied cognition with the PROMIS v1.0- Applied Cognition Abilities SF 8a
- 16
- 17 7. Baseline sleep quality with the PROMIS-4A
- 18
- 19
- 20
- 21
- 22

## 23 **Intervention**

24 We will randomly allocate patients to receive placebo or dexmedetomidine nightly during  
25 their CSICU stay. All clinical care during preoperative, intraoperative and postoperative periods  
26 will follow normal standard of care. However, trial patients admitted to the CSICU and extubated  
27 at least 30 minutes prior to 8.30 PM would receive a sleep induction dose of dexmedetomidine  
28 (1mcg/kg over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients  
29 admitted to the CSICU and extubated after 8.30 PM, but before 2 AM, would receive a sleep  
30 induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the  
31 rest of the CSICU stay the sleep induction time will be targeted for 9 PM. Trial patients who are  
32 admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following  
33 day, assuming they are extubated within 12 hours of admission to the CSICU. The maximum  
34 dexmedetomidine dose that will be administered at any one instance is 80 mcg. Clinicians will  
35 be asked to refrain from routinely administering dexmedetomidine to patients in the operating  
36 room and in the CSICU. Otherwise, all other care decisions will be at the discretion of the  
37 clinical care team.

## 38 **Outcomes**

### 39 **Primary outcome**

1  
2  
3 The primary outcome measure for this trial is the incidence delirium in the CSICU on  
4 postoperative day 1. Delirium assessments will be conducted twice daily (AM and PM with at  
5 least 6 hours between tests) beginning on postoperative day 1 using the Long Confusion  
6 Assessment Method (CAM).<sup>64 65</sup> Trial staff blinded to treatment assignments will perform the  
7 delirium assessments. A combination of the 3D-CAM and the abbreviated Montreal cognitive  
8 assessment conducted at baseline includes all the cognitive domains that are captured by the  
9 long-CAM. Thus, long-CAM results will be benchmarked against these baseline data for delirium  
10 scoring (i.e. change from baseline). Patients who elect to withdraw from the study during their  
11 hospital stay will be re-approached by the study team within 8-24 hours of study withdrawal. The  
12 study team member will elicit the reason for study discontinuation and confirm the withdrawal  
13 decision. This visit serves to ensure that the withdrawal decision was made during an informed  
14 and non-delirious cognitive state. In the event that a patient finds it difficult to complete an  
15 assessment (i.e. pain, clinical intervention), only the long-CAM domains necessary to dispel the  
16 presence of delirium will be assessed (i.e. acute onset, inattention, disorganized thinking and  
17 altered level of consciousness). Patients who cannot complete this shortened assessment will  
18 be re-approached several hours later. Long-CAM assessments for patients who are reintubated  
19 for clinical care or for further surgical management will be considered missing data.

### 20 21 22 **Secondary outcomes (in-hospital)**

23  
24  
25 Blinded trial staff will collect secondary outcomes during hospital admission. These  
26 outcomes include:

- 27  
28 1. ICU and hospital delirium/coma-free days assessed twice daily until postoperative day 3.  
29  
30 Delirious patients will be assessed until postoperative day 5. In the event that delirium  
31  
32 does not resolve by postoperative day 5, assessments will continue until postoperative  
33  
34 day 7 or hospital discharge.
- 35  
36 2. Severity of delirium scored using the CAM delirium severity scoring long form
- 37  
38 3. Date of hospital discharge and length of hospital stay assessed by chart review

4. Inpatient mortality and major inpatient morbidity assessed by chart review

### **Secondary outcomes (post-discharge)**

Blinded trial staff will collect secondary outcomes via telephone interviews and/or online questionnaires at 30-days, 90-days, and 180-days post procedure. These outcomes include:

1. Cognitive function using the abbreviated Montreal Cognitive Assessment
2. Physical function with the PROMIS SF v1.2 - Physical Function 8b
3. General health with the PROMIS SF v1.1 - Global
4. Pain with the PROMIS SF v1.0- Pain Interference 8a
5. Applied cognition with the PROMIS v1.0 - Applied Cognition Abilities SF 8a
6. Sleep quality with the PROMIS v1.0 - Sleep Disturbance 4A
7. Mortality assessed by chart review, and/or elicited from family member during follow-up calls

### **Sample size planning**

The primary objective of this trial is to detect a difference in the incidence of delirium between the dexmedetomidine-induced sleep and normal care groups. Assuming a delirium event rate of 15%, a type I error of 0.05, and power of 0.90, an  $n = 184$  patients per group will enable us to detect an absolute difference 10% (i.e., 15% versus 5%; Table 1). With respect to morbidity and healthcare costs, any observable decrease in delirium rates is clinically meaningful. Therefore, we will recruit 370 patients.

### **Recruitment**

This study will be performed at the Massachusetts General Hospital in Boston, MA. Subjects will be recruited through the cardiac surgery preoperative clinic and all enrolled patients will provide written informed consent. Informed consent for this protocol will follow a two-part process. First, a verbal consent will be obtained at the pre-operative visit prior to administering pre-operative baseline questionnaires. During this visit, the trial protocol will be



1  
2  
3 explained to potential participants. In addition, a flyer detailing an overview of the trial protocol,  
4 as well as a copy of the formal consent form, will be given to potential trial participants to take  
5 home. A study physician will obtain final, written consent on the day of surgery (typically within  
6 14 days of the pre-operative visit). After written consent is obtained, the trial team will allocate a  
7 trial identification number to the subject based on the trial stratification schema. A clinical trial  
8 pharmacist will perform central allocation into study arms according to the randomization key  
9 that is associated with each trial identification number.  
10  
11  
12  
13  
14  
15  
16

### 17 **Allocation**

18  
19 Eligible patients who provide written informed consent will be randomized to receive  
20 either dexmedetomidine or placebo with a 1:1 allocation as per a computer-generated  
21 randomization schedule generated by an independent statistician, and stratified by cardiac  
22 surgery type (i.e. valvular repair versus non-valvular repair) using permuted blocks of random  
23 sizes. The block sizes will not be disclosed until the primary endpoint is analyzed to ensure  
24 concealment. Allocation concealment is further ensured by the fact that dexmedetomidine and  
25 placebo cannot be distinguished on the basis of appearance. The randomization key that is  
26 associated with each participant trial identification number will remain with the clinical trial  
27 pharmacist (AD) for the duration of the study. Thus, the clinical trial pharmacist will conduct  
28 randomization throughout the study in order to keep the data management team and the  
29 statistician blind. All trial medications will be labeled as “dexmedetomidine or placebo,” to  
30 preserve the integrity of randomization assignments. Thus, randomization into any study arm  
31 will be conducted without any influence of the study investigators, biostatisticians, and outcome  
32 assessors. The CSICU nurse taking care of the patient will administer the trial medication. If  
33 other medications are indicated for the treatment of delirium, the treating physician will prescribe  
34 this as part of standard clinical care.  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51

### 52 **Blinding**

1  
2  
3 Assessors who are blind to treatment allocation will conduct all primary and secondary outcome  
4 assessments. To maintain the overall quality and legitimacy of the clinical trial, code breaks will  
5 occur only in exceptional circumstances when knowledge of the actual treatment is deemed  
6 essential by the treating physicians for further management of the patient. The treating  
7 physician will be directed to the clinical trial pharmacist to obtain the actual treatment code. The  
8 study investigators will maintain blindness and the treatment allocation. Additionally, the treating  
9 physician will be directed to abstain from written or verbal disclosure of the code. The principal  
10 investigator (PI) will report all code breaks to the DSMB.  
11  
12  
13  
14  
15  
16  
17  
18

### 19 20 **Criteria for patient discontinuation**

21 Patients may be discontinued from trial treatment and assessments for several reasons.  
22 These include: voluntary discontinuation by the patient, safety reasons (i.e. active hemorrhage)  
23 as judged by the clinical and/or trial physicians, failure to maintain study eligibility during the  
24 hospital stay or non-compliance with the protocol as judged by the trial physician.  
25  
26  
27  
28  
29

### 30 **Data analysis**

31 All trial outcomes will be evaluated using a modified intention-to-treat analysis plan.  
32 Hypothesis tests will be performed using a two-sided significance level (type I error) of  $\alpha=0.05$ .  
33 Sensitivity analyses using the actual treatment received will also be performed and compared  
34 with the intention-to-treat analysis results. Additional sensitivity analyses will be performed to  
35 assess the potential impact of missing data due to follow-up losses. The primary outcome will  
36 be evaluated using logistic regression examining the presence or absence of delirium  
37 conditional on randomized group assignment. Any randomization imbalances, or other potential  
38 treatment effect modifiers will be further examined as covariates in sensitivity analyses.  
39 Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will  
40 use Pearson  $\chi^2$  tests to compare categorical variables between the 2 trial groups and  
41 independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event  
42 analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 care on mortality, and CSICU and hospital lengths of stay. Kaplan-Meier survival curves will be  
4  
5 used for graphical presentation of these time-to-event analyses, and log-rank statistics will be  
6  
7 used to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients  
8  
9 will be censored at the time of last contact alive. Censoring for CSICU or hospital discharge  
10  
11 readiness analyses will occur at time of death or trial withdrawal. Because missing data rarely  
12  
13 occur entirely at random, we will assess the associations between patient characteristics with  
14  
15 respect to missing data. If patients with at least one missing outcome value are different from  
16  
17 those with complete outcomes data, we will use multiple imputation to assign values to missing  
18  
19 data risk factors and outcomes in regression modeling.  
20  
21

### 22 **Heterogeneity of treatment effects**

23  
24 Subgroup comparisons will be conducted for heterogeneity of treatment-covariate  
25  
26 interactions if the sample sizes and numbers of events within these subgroups are sufficient for  
27  
28 analysis. If there is a treatment difference together with evidence of heterogeneity, relevant  
29  
30 covariates and interaction terms will be added to the relevant regression models for formal  
31  
32 significance testing. For the primary outcome, we plan for analyses of treatment effects within  
33  
34 pre-specified subgroups potentially defined by:  
35  
36

- 37 1. Surgery type
- 38 2. Length of cardiopulmonary bypass
- 39 40 3. Presence of significant cardiac dysfunction (ejection fraction less than 35%)
- 41 42 4. Sedative administration in the ICU
- 43 44 5. Opioid administration in the ICU
- 45 46 6. Pain scores
- 47 48 7. Baseline cognitive status
- 49 50 8. Organ failure
- 51 52 9. Postoperative cerebrovascular disease
- 53 54 55 56 57 58 59 60

## 10. APACHE/EUROscore

### **Interim analyses**

Interim efficacy data will be provided to the Data Safety Monitoring Board (DSMB) during yearly meetings to permit benefit-to-risk assessments. An independent statistician that is unblinded to the treatment allocation will perform the interim-analysis. The statistician will report to the DSMB in a closed session. Thus, the DSMB will have unblinded access to all data to inform recommendations. If at any time during the course of the study the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

### **Data management**

All data collected for the MINDDDS trial will be entered into the Massachusetts General Hospital Research Electronic Data Capture (REDCap) application.<sup>66</sup> Data entered into the database will be retrievable for viewing through the data entry applications. Data integrity will be enforced through referential data rules, valid values, range checks, and consistency checks against data already stored in the database. Programs designed to detect missing data or specific errors in the data will be implemented to detect additional errors. These errors will be summarized along with detailed descriptions for each specific problem in monthly Data Query Reports, which will be sent to the PI. The PI will respond by checking the original forms for inconsistency, checking other sources to determine the correction, modifying the original forms as necessary, and entering a response to the query. Data access will be restricted via password protection to only those individuals who are authorized to work on the trial. Specific privilege assignments within the database will also be employed to limit the types of data that authorized users may access to the minimum required by their role in the trial. Electronic audit trails will be used to capture and record changes to database contents automatically. Original study forms will also be kept in files. Participant files will be stored in numerical order in a secure and

1  
2  
3 accessible place and manner. These files will be maintained in storage for a period of at least 5  
4 years after study completion. Members of the adjudication committee will request a subset of  
5 these study forms later for quality control.  
6  
7  
8  
9

### 10 **Site training**

11  
12 Trial team members have undergone a rigorous CAM training program led by a  
13 neuropsychologist and member of the team that created the Long-CAM.<sup>65</sup> The CAM is the most  
14 widely used delirium assessment tool in the research setting, with a high sensitivity and  
15 specificity when compared with formal psychiatric diagnosis.<sup>64 65</sup> The 3D-CAM is a three-minute  
16 assessment tool for delirium, which has good agreement with the CAM.<sup>67</sup> All CAM assessors  
17 will be required to score CAM interview videos depicting delirious and non-delirious patients.  
18 Team members that attended the initial CAM training program will oversee the training of new  
19 team members. Trainees will be required to observe CAM interviews conducted by previously  
20 trained team members, and to agree with the trainer on the presence or absence of cognitive  
21 features assessed by the CAM on a minimum of six interviews. Newly trained team members  
22 will be required to conduct their first CAM assessment of a MINDDS trial patient in the presence  
23 of a previously trained team member.  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

### 38 **Data and safety monitoring**

39 All unexpected adverse events that are related to the trial treatment will be recorded in  
40 the trial database and reported as required to the Partners Healthcare IRB. A data and safety  
41 monitoring board (DSMB) will also oversee the MINDDS trial. The DSMB will provide  
42 independent oversight of the MINDDS, and will review general conduct of the trial and trial data  
43 for participant safety. The DSMB is comprised of independent, multidisciplinary experts who will  
44 make recommendations regarding the continuation, modification, or termination of the trial for  
45 harm from intervention. The members will have the requisite expertise to examine accumulating  
46 data, to protect the integrity of the clinical experiments to which the patients have consented to  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 participate, and to assure the regulatory bodies, the public and the National Institutes of Health  
4 that conflicts of interest do not compromise either patient safety or trial integrity. The DSMB will  
5 convene before trial initiation and annually to review safety events. Recommendations from the  
6 DSMB for protocol modifications or revisions will be communicated through a representative of  
7 the National Institutes on Aging to the PI.  
8  
9  
10  
11  
12

13  
14 The study operations committee will determine relatedness of an event to the study drug  
15 based on a temporal relationship to the study drug administration, whether the event is  
16 unexpected given the clinical course, previous medical conditions, and concomitant  
17 medications. They will communicate to adverse events to members of the study steering  
18 committee for additional review. The study steering committee will perform expedited reviews  
19 for all events that meet the FDAs definition of SAEs. They will also perform expedited reviews  
20 for any event that a study investigator or the DSMB judges to impose a significant hazard,  
21 contraindication, or side effect. All SAEs will be reported to the DSMB along with all relevant  
22 event and outcome information. The DSMB will be notified by e-mail within 2 days of the  
23 occurrence of any SAE and a formal review will be performed to determine relatedness to the  
24 study. Additional reporting to the IRB will be done within 24 hours of the SAE. All patients that  
25 experience a SAE will be censored from the study at SAE occurrence.  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38

### 39 **Data Monitoring and Quality Assurance**

40  
41 Reflective of the state of the art in clinical trials, the MINDDDS trial will employ a web-  
42 based portal for data quality and completeness. The portal will display in real time the following  
43 variables for all patients: sex, race, adverse events, study related data etc.  
44  
45  
46

### 47 **Trial risks**

48  
49 The risk of a breach of confidentiality is small and all possible efforts have been taken to  
50 ensure the security of trial data and minimize the risks of accidental disclosure of identifiable  
51 data elements. The risks associated with dexmedetomidine are related to drug induced  
52 reduction in sympathetic activity, resulting in hypotension and bradycardia. However,  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 cardiovascular parameters are continuously monitored in the CSICU, ensuring that appropriate  
4 medical intervention can be instituted in a timely fashion for clinically significant hypotensive or  
5 bradycardic episodes. Thus, the risk of clinically significant hypotension or bradycardia in our  
6 patient study population is small.  
7  
8  
9

### 11 **Ethics and dissemination**

12  
13  
14 The Partners Health Care IRB has approved the trial. The trial steering committee will be  
15 responsible for all major decisions regarding changes to the protocol. The committee will  
16 communicate these changes to the IRB and the DSMB. Electronic data and demographic  
17 information will be accessed only as necessary for completion of trial follow-up tasks. The PI  
18 has will have access to all data. The primary papers emanating from MINDDDS will present  
19 primary and secondary outcome. Secondary analyses will also be conducted to construct  
20 predictive models for delirium occurrence and resource utilization. Mechanistic manuscripts on  
21 the pathophysiology of delirium from sub-studies (i.e. electroencephalogram dynamics,  
22 biomarker discovery, brain imaging) will also be published. Dissemination plans include  
23 presentations at local, national and international scientific conferences. Every effort will be  
24 made to publish results of the MINDDDS trial in a peer-reviewed journal. Dissemination of results  
25 to trial participants and their family members will be available upon request. Updates and results  
26 of the trial will be available to the public at [clinicaltrials.gov](http://clinicaltrials.gov).  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40

41 In summary, the MINDDDS trial will evaluate a new preemptive therapeutic sleep strategy  
42 for the prevention of delirium, and may enable new insights into the pathophysiology of delirium.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## References

1. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *Journal of the American Geriatrics Society* 2010;58(4):643-9. doi: 10.1111/j.1532-5415.2010.02762.x [published Online First: 2010/03/30]
2. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. Washington, D.C.: American Psychiatric Association 2013.
3. Hamilton GM, Wheeler K, Di Michele J, et al. A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality. *Anesthesiology* 2017;127(1):78-88. doi: 10.1097/ALN.0000000000001660
4. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2013;21(12):1190-222. doi: 10.1016/j.jagp.2013.09.005 [published Online First: 2013/11/12]
5. Shearer WT, Reuben JM, Mullington JM, et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *The Journal of allergy and clinical immunology* 2001;107(1):165-70. doi: 10.1067/mai.2001.112270
6. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* 2007;30(9):1145-52.
7. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *The Journal of clinical endocrinology and metabolism* 2004;89(5):2119-26. doi: 10.1210/jc.2003-031562
8. Johns MW, Large AA, Masterton JP, et al. Sleep and delirium after open heart surgery. *The British journal of surgery* 1974;61(5):377-81. [published Online First: 1974/05/01]
9. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Critical care medicine* 2002;30(3):536-40. [published Online First: 2002/05/07]
10. Munster BC, Aronica E, Zwinderman AH, et al. Neuroinflammation in delirium: a postmortem case-control study. *Rejuvenation research* 2011;14(6):615-22. doi: 10.1089/rej.2011.1185
11. Siami S, Annane D, Sharshar T. The encephalopathy in sepsis. *Critical care clinics* 2008;24(1):67-82, viii. doi: 10.1016/j.ccc.2007.10.001
12. O'Keefe ST, Ni Chonchubhair A. Postoperative delirium in the elderly. *British journal of anaesthesia* 1994;73(5):673-87.
13. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. *Injury* 2007;38(12):1336-45. doi: 10.1016/j.injury.2007.10.003
14. Shimaoka M, Park EJ. Advances in understanding sepsis. *European journal of anaesthesiology Supplement* 2008;42:146-53. doi: 10.1017/S0265021507003389
15. Weichhart T, Haidinger M, Horl WH, et al. Current concepts of molecular defence mechanisms operative during urinary tract infection. *European journal of clinical investigation* 2008;38 Suppl 2:29-38. doi: 10.1111/j.1365-2362.2008.02006.x
16. Bjornsson GL, Thorsteinsson L, Gudmundsson KO, et al. Inflammatory cytokines in relation to adrenal response following total hip replacement. *Scandinavian journal of immunology* 2007;65(1):99-105. doi: 10.1111/j.1365-3083.2006.01872.x
17. Kraghsbjerg P, Holmberg H, Vikorfors T. Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. *The European journal of surgery = Acta chirurgica* 1995;161(1):17-22.
18. Keck M, Herndon DH, Kamolz LP, et al. Pathophysiology of burns. *Wiener medizinische Wochenschrift* 2009;159(13-14):327-36. doi: 10.1007/s10354-009-0651-2

19. Marx N, Neumann FJ, Ott I, et al. Induction of cytokine expression in leukocytes in acute myocardial infarction. *Journal of the American College of Cardiology* 1997;30(1):165-70.
20. Asimakopoulos G. Mechanisms of the systemic inflammatory response. *Perfusion* 1999;14(4):269-77.
21. Sun Y, Tawara I, Toubai T, et al. Pathophysiology of acute graft-versus-host disease: recent advances. *Translational research : the journal of laboratory and clinical medicine* 2007;150(4):197-214. doi: 10.1016/j.trsl.2007.06.003
22. Stinghen AE, Goncalves SM, Martines EG, et al. Increased plasma and endothelial cell expression of chemokines and adhesion molecules in chronic kidney disease. *Nephron Clinical practice* 2009;111(2):c117-26. doi: 10.1159/000191205
23. Shawcross DL, Shabbir SS, Taylor NJ, et al. Ammonia and the neutrophil in the pathogenesis of hepatic encephalopathy in cirrhosis. *Hepatology* 2010;51(3):1062-9. doi: 10.1002/hep.23367
24. van Munster BC, Korevaar JC, Zwinderman AH, et al. Time-course of cytokines during delirium in elderly patients with hip fractures. *Journal of the American Geriatrics Society* 2008;56(9):1704-9. doi: 10.1111/j.1532-5415.2008.01851.x
25. Culley DJ, Snayd M, Baxter MG, et al. Systemic inflammation impairs attention and cognitive flexibility but not associative learning in aged rats: possible implications for delirium. *Frontiers in aging neuroscience* 2014;6:107. doi: 10.3389/fnagi.2014.00107
26. Cerejeira J, Firmino H, Vaz-Serra A, et al. The neuroinflammatory hypothesis of delirium. *Acta neuropathologica* 2010;119(6):737-54. doi: 10.1007/s00401-010-0674-1 [published Online First: 2010/03/24]
27. Norden DM, Godbout JP. Review: microglia of the aged brain: primed to be activated and resistant to regulation. *Neuropathology and applied neurobiology* 2013;39(1):19-34. doi: 10.1111/j.1365-2990.2012.01306.x [published Online First: 2012/10/09]
28. Cunningham C. Systemic inflammation and delirium: important co-factors in the progression of dementia. *Biochemical Society transactions* 2011;39(4):945-53. doi: 10.1042/BST0390945 [published Online First: 2011/07/27]
29. Rosenberg-Adamsen S, Kehlet H, Dodds C, et al. Postoperative sleep disturbances: mechanisms and clinical implications. *British journal of anaesthesia* 1996;76(4):552-9. [published Online First: 1996/04/01]
30. Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *British medical journal* 1985;290(6474):1029-32. [published Online First: 1985/04/06]
31. Ellis BW, Dudley HA. Some aspects of sleep research in surgical stress. *Journal of psychosomatic research* 1976;20(4):303-8. [published Online First: 1976/01/01]
32. Kavey NB, Ahshuler KZ. Sleep in herniorrhaphy patients. *American journal of surgery* 1979;138(5):683-7. [published Online First: 1979/11/01]
33. Lehmkuhl P, Prass D, Pichlmayr I. General anesthesia and postnarcotic sleep disorders. *Neuropsychobiology* 1987;18(1):37-42. doi: 118390 [published Online First: 1987/01/01]
34. Akeju O, Brown EN. Neural oscillations demonstrate that general anesthesia and sedative states are neurophysiologically distinct from sleep. *Curr Opin Neurobiol* 2017;44:178-85. doi: 10.1016/j.conb.2017.04.011
35. Akeju O, Hobbs LE, Gao L, et al. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: A pilot study. *Clin Neurophysiol* 2017;129(1):69-78. doi: 10.1016/j.clinph.2017.10.005
36. van Lier H, Drinkenburg WH, van Eeten YJ, et al. Effects of diazepam and zolpidem on EEG beta frequencies are behavior-specific in rats. *Neuropharmacology* 2004;47(2):163-74. doi: 10.1016/j.neuropharm.2004.03.017 [published Online First: 2004/06/30]

- 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
  - 10
  - 11
  - 12
  - 13
  - 14
  - 15
  - 16
  - 17
  - 18
  - 19
  - 20
  - 21
  - 22
  - 23
  - 24
  - 25
  - 26
  - 27
  - 28
  - 29
  - 30
  - 31
  - 32
  - 33
  - 34
  - 35
  - 36
  - 37
  - 38
  - 39
  - 40
  - 41
  - 42
  - 43
  - 44
  - 45
  - 46
  - 47
  - 48
  - 49
  - 50
  - 51
  - 52
  - 53
  - 54
  - 55
  - 56
  - 57
  - 58
  - 59
  - 60
37. Feinberg I, Maloney T, Campbell IG. Effects of hypnotics on the sleep EEG of healthy young adults: new data and psychopharmacologic implications. *Journal of psychiatric research* 2000;34(6):423-38. [published Online First: 2001/02/13]
38. Patat A, Trocherie S, Thebault JJ, et al. EEG profile of intravenous zolpidem in healthy volunteers. *Psychopharmacology* 1994;114(1):138-46. [published Online First: 1994/02/01]
39. Akeju O, Pavone KJ, Westover MB, et al. A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. *Anesthesiology* 2014;121(5):978-89. doi: 10.1097/ALN.0000000000000419 [published Online First: 2014/09/05]
40. Akeju O, Westover MB, Pavone KJ, et al. Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. *Anesthesiology* 2014;121(5):990-8. doi: 10.1097/ALN.0000000000000436 [published Online First: 2014/09/19]
41. Purdon PL, Pierce ET, Mukamel EA, et al. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proceedings of the National Academy of Sciences of the United States of America* 2013;110(12):E1142-51. doi: 10.1073/pnas.1221180110 [published Online First: 2013/03/15]
42. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society* 2012;60(4):616-31. doi: 10.1111/j.1532-5415.2012.03923.x
43. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology* 1992;76(6):948-52. [published Online First: 1992/06/01]
44. Lu J, Nelson LE, Franks N, et al. Role of endogenous sleep-wake and analgesic systems in anesthesia. *The Journal of comparative neurology* 2008;508(4):648-62. doi: 10.1002/cne.21685 [published Online First: 2008/04/03]
45. Mizobe T, Maghsoudi K, Sitwala K, et al. Antisense technology reveals the alpha2A adrenoceptor to be the subtype mediating the hypnotic response to the highly selective agonist, dexmedetomidine, in the locus coeruleus of the rat. *The Journal of clinical investigation* 1996;98(5):1076-80. doi: 10.1172/JCI118887 [published Online First: 1996/09/01]
46. Nacif-Coelho C, Correa-Sales C, Chang LL, et al. Perturbation of ion channel conductance alters the hypnotic response to the alpha 2-adrenergic agonist dexmedetomidine in the locus coeruleus of the rat. *Anesthesiology* 1994;81(6):1527-34. [published Online First: 1994/12/01]
47. Nelson LE, Lu J, Guo T, et al. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003;98(2):428-36. [published Online First: 2003/01/29]
48. Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta anaesthesiologica Scandinavica* 2008;52(2):289-94. doi: 10.1111/j.1399-6576.2007.01537.x [published Online First: 2007/11/17]
49. Alexopoulou C, Kondili E, Diamantaki E, et al. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study. *Anesthesiology* 2014;121(4):801-7. doi: 10.1097/ALN.0000000000000361 [published Online First: 2014/07/06]
50. Oto J, Yamamoto K, Koike S, et al. Sleep quality of mechanically ventilated patients sedated with dexmedetomidine. *Intensive care medicine* 2012;38(12):1982-9. doi: 10.1007/s00134-012-2685-y [published Online First: 2012/09/11]

- 1
- 2
- 3
- 4 51. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of
- 5 critically ill patients: a randomized trial. *Jama* 2009;301(5):489-99. doi:
- 6 10.1001/jama.2009.56 [published Online First: 2009/02/04]
- 7 52. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs
- 8 lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS
- 9 randomized controlled trial. *Jama* 2007;298(22):2644-53. doi: 10.1001/jama.298.22.2644
- 10 [published Online First: 2007/12/13]
- 11 53. Reade MC, Eastwood GM, Bellomo R, et al. Effect of Dexmedetomidine Added to Standard
- 12 Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical
- 13 Trial. *Jama* 2016;316(7):773-4. doi: 10.1001/jama.2016.2707 [published Online First:
- 14 2016/03/16]
- 15 54. Maldonado JR, Wysong A, van der Starre PJ, et al. Dexmedetomidine and the reduction of
- 16 postoperative delirium after cardiac surgery. *Psychosomatics* 2009;50(3):206-17. doi:
- 17 10.1176/appi.psy.50.3.206 [published Online First: 2009/07/02]
- 18 55. Wafford KA, Ebert B. Emerging anti-insomnia drugs: tackling sleeplessness and the quality
- 19 of wake time. *Nature reviews Drug discovery* 2008;7(6):530-40. doi: 10.1038/nrd2464
- 20 [published Online First: 2008/05/31]
- 21 56. Huber R, Ghilardi MF, Massimini M, et al. Local sleep and learning. *Nature*
- 22 2004;430(6995):78-81. doi: 10.1038/nature02663 [published Online First: 2004/06/09]
- 23 57. Huber R, Ghilardi MF, Massimini M, et al. Arm immobilization causes cortical plastic
- 24 changes and locally decreases sleep slow wave activity. *Nature neuroscience*
- 25 2006;9(9):1169-76. doi: 10.1038/nn1758 [published Online First: 2006/08/29]
- 26 58. Huber R, Tononi G, Cirelli C. Exploratory behavior, cortical BDNF expression, and sleep
- 27 homeostasis. *Sleep* 2007;30(2):129-39. [published Online First: 2007/03/01]
- 28 59. Rasch B, Buchel C, Gais S, et al. Odor cues during slow-wave sleep prompt declarative
- 29 memory consolidation. *Science* 2007;315(5817):1426-9. doi: 10.1126/science.1138581
- 30 [published Online First: 2007/03/10]
- 31 60. Backhaus J, Junghanns K, Born J, et al. Impaired declarative memory consolidation during
- 32 sleep in patients with primary insomnia: Influence of sleep architecture and nocturnal
- 33 cortisol release. *Biological psychiatry* 2006;60(12):1324-30. doi:
- 34 10.1016/j.biopsych.2006.03.051 [published Online First: 2006/08/01]
- 35 61. Molle M, Marshall L, Gais S, et al. Learning increases human electroencephalographic
- 36 coherence during subsequent slow sleep oscillations. *Proceedings of the National*
- 37 *Academy of Sciences of the United States of America* 2004;101(38):13963-8. doi:
- 38 10.1073/pnas.0402820101 [published Online First: 2004/09/10]
- 39 62. Prehn-Kristensen A, Munz M, Goder R, et al. Transcranial oscillatory direct current
- 40 stimulation during sleep improves declarative memory consolidation in children with
- 41 attention-deficit/hyperactivity disorder to a level comparable to healthy controls. *Brain*
- 42 *stimulation* 2014;7(6):793-9. doi: 10.1016/j.brs.2014.07.036 [published Online First:
- 43 2014/08/26]
- 44 63. Marshall L, Molle M, Hallschmid M, et al. Transcranial direct current stimulation during sleep
- 45 improves declarative memory. *The Journal of neuroscience : the official journal of the*
- 46 *Society for Neuroscience* 2004;24(44):9985-92. doi: 10.1523/JNEUROSCI.2725-
- 47 04.2004 [published Online First: 2004/11/05]
- 48 64. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment
- 49 method. A new method for detection of delirium. *Annals of internal medicine*
- 50 1990;113(12):941-8. [published Online First: 1990/12/15]
- 51 65. Ramaswamy R, Dix EF, Drew JE, et al. Beyond grand rounds: a comprehensive and
- 52 sequential intervention to improve identification of delirium. *The Gerontologist*
- 53 2011;51(1):122-31. doi: 10.1093/geront/gnq075
- 54
- 55
- 56
- 57
- 58
- 59
- 60



- 1  
2  
3 66. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a  
4 metadata-driven methodology and workflow process for providing translational research  
5 informatics support. *Journal of biomedical informatics* 2009;42(2):377-81. doi:  
6 10.1016/j.jbi.2008.08.010 [published Online First: 2008/10/22]  
7  
8 67. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-  
9 minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test  
10 study. *Annals of internal medicine* 2014;161(8):554-61. doi: 10.7326/M14-0865  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Table 1.** Numeric Results for Testing Two Proportions using the Z-Test with Unpooled Variance

Target Power	Actual Power	Sample size group 1	Sample size group 2	Total sample size	Proportion group 1	Proportion group 2	Difference between proportions	Alpha
<b>0.80</b>	0.80687	56	56	112	0.01	0.15	0.14	0.05
<b>0.90</b>	0.90131	74	74	148	0.01	0.15	0.14	0.05
<b>0.80</b>	0.80388	69	69	138	0.02	0.15	0.13	0.05
<b>0.90</b>	0.90167	92	92	184	0.02	0.15	0.13	0.05
<b>0.80</b>	0.80183	138	138	276	0.05	0.15	0.10	0.05
<b>0.90</b>	0.90019	184	184	368	0.05	0.15	0.10	0.05
<b>0.80</b>	0.80009	683	683	1366	0.10	0.15	0.05	0.05
<b>0.90</b>	0.90027	915	915	1830	0.10	0.15	0.05	0.05
<b>0.80</b>	0.80010	1106	1106	2212	0.11	0.15	0.04	0.05
<b>0.90</b>	0.90015	1481	1481	2962	0.11	0.15	0.04	0.05
<b>0.80</b>	0.80003	2033	2033	4066	0.12	0.15	0.03	0.05
<b>0.90</b>	0.90006	2722	2722	5444	0.12	0.15	0.03	0.05
<b>0.80</b>	0.80008	4722	4722	9444	0.13	0.15	0.02	0.05
<b>0.90</b>	0.90004	6321	6321	12642	0.13	0.15	0.02	0.05
<b>0.80</b>	0.80001	19458	19458	38916	0.14	0.15	0.01	0.05
<b>0.90</b>	0.90000	26048	26048	52096	0.14	0.15	0.01	0.05

**STUDY TEAM ROSTER****Principal****Investigator:****Oluwaseun Johnson-Akeju, M.D., M.M.Sc.**

Massachusetts General Hospital

Department of Anesthesiology

55 Fruit Street

Gray/Jackson 444

Boston, MA 02114

United States

617-724-2000

oluwaseun.akeju@mgh.harvard.edu

**Co-Investigators:****Federico Bilotta, MD**

University of Rome 'La Sapienza'

Department of Anesthesiology

Piazzale Aldo Moro,

5, 00185 Roma, Italy

339 33 708 22

bilotta@tiscali.it

**Emery N. Brown, M.D., Ph.D.**

Massachusetts General Hospital

Department of Anesthesiology

55 Fruit Street

Gray/Jackson 444

Boston, MA 02114

United States

617-324-1880

enb@neurostat.mit.edu

**Gaston Cudemus, M.D.**

Massachusetts General Hospital

Department of Anesthesiology

55 Fruit Street

Gray/Jackson 444

Boston, MA 02114

United States

617-726-9149

gcudemus@mgh.harvard.edu

**David D'Alessandro, M.D.**

Massachusetts General Hospital

Department of Surgery



1  
2  
3 Division of Cardiac Surgery  
4 Cox Building 644  
5 Boston, MA 02114  
6 United States  
7  
8 617-726-8841  
9 dadalessandro@mgh.harvard.edu  
10

11 **Hao Deng, M.D., M.P.H.**

12 Massachusetts General Hospital  
13 Department of Anesthesiology  
14 55 Fruit Street  
15 Gray/Jackson 444  
16 Boston, MA 02114  
17 United States  
18  
19 617-643-6757  
20 hdeng1@mgh.harvard.edu  
21  
22

23 **Alan DiBiasio, B.S. Pharm**

24 Massachusetts General Hospital  
25 Department of Pharmacy,  
26 55 Fruit St  
27 Gray/Bigelow 005  
28 Boston, MA 02114  
29 United States  
30  
31 617-724-1270  
32 adibiasio@partners.org  
33  
34

35 **Jacob A Gitlin, B.S.**

36 Massachusetts General Hospital  
37 Department of Anesthesiology  
38 55 Fruit Street  
39 Gray/Jackson 444  
40 Boston, MA 02114  
41 United States  
42  
43 617-724-2000  
44 jgitlin1@partners.org  
45

46 **Eunice Y Hahm, B.S**

47 Massachusetts General Hospital  
48 Department of Anesthesiology  
49 55 Fruit Street  
50 Gray/Jackson 444  
51 Boston, MA 02114  
52 United States  
53  
54 617-724-2000  
55 ehahm@mgh.harvard.edu  
56  
57  
58  
59  
60

**Lauren E. Hobbs, M.S.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-724-9857  
[lehobbs@mgh.harvard.edu](mailto:lehobbs@mgh.harvard.edu)

**Timothy Houle, Ph.D.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-724-2111  
[thoule1@mgh.harvard.edu](mailto:thoule1@mgh.harvard.edu)

**Reine Ibala, B.S.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-724-2000  
[ribala@mgh.harvard.edu](mailto:ribala@mgh.harvard.edu)

**Marco L. Loggia, Ph.D.**

Massachusetts General Hospital  
Department of Radiology  
149 13th Street  
CNY - Building 149  
Charlestown, MA 02129  
United States  
617-643-7267  
[marco.loggia@mgh.harvard.edu](mailto:marco.loggia@mgh.harvard.edu)

**Jason Qu, M.D.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-643-4401  
[jqu@partners.org](mailto:jqu@partners.org)

**Kara J. Pavone, B.S., B.S.N., R.N.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-724-9857  
kpavone@mgh.harvard.edu

**Shahzad Shaefi, M.D., MPH**

Beth Israel Deaconess Medical Center  
Department of Anesthesia and Critical Care  
330 Brookline Avenue,  
Feldberg 407  
Boston, MA 02215  
United States  
617-667-3112  
sshafefi@bidmc.harvard.edu

**Kenneth Shelton, M.D.**

Massachusetts General Hospital  
Department of Anesthesiology  
55 Fruit Street  
Gray/Jackson 444  
Boston, MA 02114  
United States  
617-726-0917  
kshelton2@partners.org

**George Tolis, M.D.**

Massachusetts General Hospital  
Department of Surgery  
Division of Cardiac Surgery  
55 Fruit Street  
Cox Building 654  
Boston, MA 02114  
United States  
617-643-9280  
gtolis@partners.org

**M. Brandon Westover, MD, PhD**

Massachusetts General Hospital  
Department of Neurology  
55 Fruit Street  
Boston, MA 02114  
United States

617-726-3311  
mwestover@mgh.harvard.edu

<b>Primary Registry and Trial Identifying Number</b>	<b>ClinicalTrials: NCT02856594</b>
<b>Date of Registration</b>	July 29 2016
<b>Secondary Identifying Numbers</b>	IRB ID#: 2016 P000742
<b>Source(s) of Monetary Support</b>	National Institute on Aging Grant (Award Reference Number R01 AG053582-01)
<b>Primary Sponsor</b>	Department of Anesthesiology, Critical care and Pain Medicine Massachusetts General Hospital Boston, MA 02114
<b>Contact name</b>	Oluwaseun Akeju, M.D., M.M.Sc oluwaseun.akeju@mgh.harvard.edu 617-724-2000 Department of Anesthesiology, Critical care and Pain Medicine Massachusetts General Hospital 55 Fruit Street Gray/Jackson 444 Boston, MA 02114 United States
<b>Contact for Scientific Queries</b>	Oluwaseun Akeju, M.D., M.M.Sc oluwaseun.akeju@mgh.harvard.edu 617-724-2000 Department of Anesthesiology Massachusetts General Hospital 55 Fruit Street Gray/Jackson 444 Boston, MA 02114 United States
<b>Public Title</b>	Protocol for the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) Trial
<b>Scientific Title</b>	Protocol for the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) Trial: a Randomized, Double blind, Parallel-arm, Placebo-controlled Clinical Trial

**Countries of Recruitment**

United States

**Health Condition(s) or Problem(s) Studied**

Postoperative delirium, predictors of delirium

**Intervention(s)**

Trial arm 1: Dexmedetomidine-induced Sleep Group (primary intervention)  
Post cardiac surgical patients admitted to the cardiac surgical intensive care unit (CSICU) and extubated at least 30 minutes prior to 8:30 PM would receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes; maximum administered dose of 80mcg at any one instance) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would receive a sleep induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the rest of the CSICU stay the dexmedetomidine administration time will be targeted for 9 PM. Trial patients admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU.

Trial arm 2: Placebo Control Group.  
Post cardiac surgical patients admitted to the CSICU and extubated at least 30 minutes prior to 8:30 PM would receive placebo (intravenous normal saline over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would receive the placebo infusion of normal saline within 30 minutes of extubation. However, throughout the rest of the CSICU stay the placebo administration time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU.

**Key Inclusion, Exclusion and Objective Drop Criteria****Inclusion Criteria**

1. Age  $\geq$  60
2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for  $\geq$  24 hours
3. Scheduled same day surgical admission

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Exclusion Criteria

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score > 5
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit due to structural or anoxic brain damage
9. Surgical procedures requiring total circulatory arrest

Objective Drop Criteria

1. Scheduled for a second surgical procedure during hospital stay
2. Post-operative intubation > 12 hours

**Trial Type**

Interventional

Allocation: Randomized

Intervention model: Parallel assignment

Blinding: Clinicians blinded to intervention, subject blinded to intervention, primary outcome assessor blinded to intervention

Assignment: Parallel

Primary purpose: Prevention

**Date of First Enrollment**

March, 2017

**Target Sample Size**

Recruiting until 370 patients receive the study intervention on Post Operative Day 0.

**Recruitment Status**

Enrolling

**Primary Outcome(s)**

Outcome name: Incidence of postoperative delirium

Method of measurement: The Long Confusion

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Key Secondary Outcomes

### Assessment Method

Time points of interest: Postoperative day 1

Outcome name: ICU and hospital delirium/coma-free days

Method of measurement: Delirium assessment with: The Long Confusion Assessment Method

Time points of interest: Up until postoperative day 3 if no delirium. Up until postoperative day 5 if delirium exhibited but resolved. Up until postoperative day 7 or discharge if delirium unresolved by postoperative day 5.

Outcome name: Severity of Delirium

Method of measurement: The Long Confusion Assessment Method

Time points of interest: Up until postoperative day 3 if no delirium. Up until postoperative day 5 if delirium exhibited but resolved. Up until postoperative day 7 or discharge if delirium unresolved by postoperative day 5.

Outcome name: Date of Hospital Discharge / Length of Hospital Stay

Method of measurement: Medical record review

Time points of interest: Up until hospital discharge

Outcome name: 30-day, 90-day, and 180-day mortality

Method of measurement: Medical record review

Time points of interest: 30 days, 90 days and 180 days postoperatively

Outcome name: Postoperative cognitive status

Method of measurement: Abbreviated Montreal Cognitive Assessment, 3D-CAM and PROMIS-29 applied cognition abilities questionnaire

Time points of interest: 30 days, 90 days and 180



1  
2  
3 days postoperatively  
4

5 Outcome name: Postoperative health related quality  
6 of life  
7

8 Method of measurement: PROMIS-29 physical  
9 function, global health, pain interference  
10 questionnaires, and sleep questionnaire  
11

12 Time points of interest: 30 days, 90 days and 180  
13 days postoperatively  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

### Principal Investigator:

Oluwaseun Akeju, M.D., M.M.Sc.

Responsibilities include: design and conduct of the MINDDS trial, preparation of protocol and revisions, organization of steering committee meetings, and publication of trial reports.

### Steering Committee:

Oluwaseun Akeju, M.D., M.M.Sc	Gaston Cudemus, M.D.	Ken Shelton, M.D.
Federico Bilotta, MD	Marco L Loggia, Ph.D.	Brandon M Westover, M.D., Ph.D.
Alan DiBiasio, Pharm.D	Kara Pavone, B.SN., R.N	Jason Qu, M.D.
Tim Houle, Ph.D	Shahzad Shaefi, M.D., MPH	

Responsibilities include: agreement of final protocol, reviewing progress of trial and if necessary, conducting changes to the protocol, coordinating with principal investigator, and communicating with trial management committee.

### Trial Management Committee:

Oluwaseun Akeju, M.D, M.M.Sc.  
Tim Houle, Ph.D.  
Lauren E Hobbs, M.S.  
Reine Ibala, B.S.  
Eunice Hahm, B.S.  
Jacob Gitlin, B.S.  
Kara Pavone, B.S.N, R.N.  
Jason Qu, M.D.  
Ken Shelton, M.D.

Responsibilities include: trial planning, organization of steering committee meetings, reporting SAEs (Serious Adverse Events) to Partners Healthcare IRB (Institutional Review Board), maintaining REDCap electronic database, reporting to steering committee, conducting data verification, recruitment, randomization, and follow-up of trial participants

### Data Management Committee:

Hao Deng, M.D., M.P.H.  
Tim Houle, Ph.D.

Responsibilities include: statistical design of trial, data verification.

### Data Adjudication Committee:

Oluwaseun Akeju, M.D., M.M.Sc.  
Shahzad Shaefi, M.D., MPH

1  
2  
3 Brandon M Westover, M.D., Ph.D.  
4

5 **Responsibilities include: regularly reviewing delirium assessments, contacting**  
6 **trial management committee, retraining researchers if necessary.**  
7

8 **Data and Safety Monitoring Committee:**  
9

10 Wie Chao, M.D., Ph.D. - University of Maryland School of Medicine

11 **Jesse Ehrenfeld, M.D.,M.P.H. -Vanderbilt University Medical Center**

12 Michael Gropper, M.D., Ph.D. - University of California San Francisco

13 Keith A. Jones, M.D. - The University of Alabama at Birmingham  
14

15 Responsibilities include: reviewing and evaluating the trial data to ensure participant  
16 safety, trial conduct, progress, and efficacy, and making recommendations regarding the  
17 continuation, modification, and termination of the trial.  
18



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1, 6
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1, 6
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 1-6 and 10, 11, 35
	5b	Name and contact information for the trial sponsor	Page 6
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Pages 10-12, 35

## Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pages 15-17
	6b	Explanation for choice of comparators	Pages 16-17?
Objectives	7	Specific objectives or hypotheses	Page 17
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 17
<b>Methods: Participants, interventions, and outcomes</b>			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 19, 22
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 19
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 18, 20, 23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 20, 22
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 19-20, 23, 28
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 20-21
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Pages 19-22

1  
2  
3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including Page 13,17, 21  
4 clinical and statistical assumptions supporting any sample size calculations

5  
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size Page 22  
7

8 **Methods: Assignment of interventions (for controlled trials)**  
9

10 Allocation:

11  
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any Pages 19, 22-24  
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
15 or assign interventions  
16

17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, Page 22, 23  
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  
19  
20

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to Page 22  
22 interventions  
23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome Pages 22-23  
25 assessors, data analysts), and how  
26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's Page 23, 25  
28 allocated intervention during the trial  
29  
30

31 **Methods: Data collection, management, and analysis**  
32

33 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related Pages 19-22, 25-  
34 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of 26  
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
36 Reference to where data collection forms can be found, if not in the protocol  
37

38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be Pages 20-21  
39 collected for participants who discontinue or deviate from intervention protocols  
40  
41  
42  
43  
44

1				
2				
3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 25-26, 28
4				
5				
6				
7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 23-24
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pages 24-25
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pages 23-24
13				
14				
15	<b>Methods: Monitoring</b>			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Pages 27-28
18				
19				
20				
21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 25
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Pages 27-28
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Pages 27-28
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 29
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Pages 27-29
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				





1				
2				
3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 22
4				
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 22
7				
8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17, 19, 21, 26, 28
9				
10				
11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10
12				
13				
14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 29
15				
16				
17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page 28
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 29
21				
22				
23				
24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	Page 10, 35
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 29
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
35				
36				

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
 40

41  
 42  
 43  
 44  
 45  
 46  
 47