INI

Therapeutic Effects of Intranasally-Administered Insulin (INI) for aMCI or Mild AD

(AKA)

Study of Nasal Insulin to Fight Forgetfulness

Project Director
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Coordinating Center
ADCS
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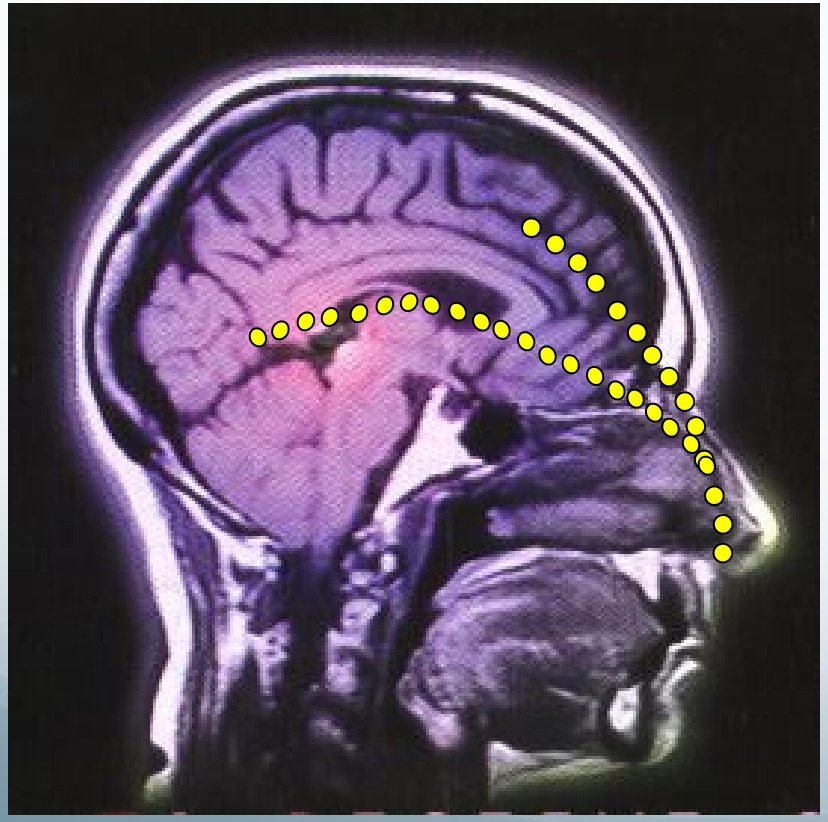
Rationale

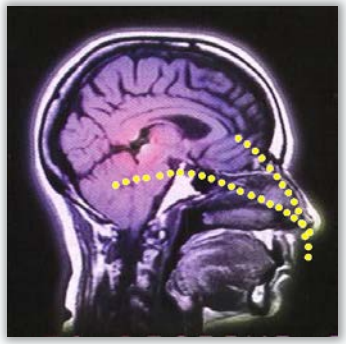
- **Insulin affects many aspects of brain function: cerebral glucose metabolism, synaptic health, amyloid regulation, tau phosphorylation, vascular function, inflammation, cognition** [De Felice et al. 2013]
- **AD patients may have brain insulin resistance or deficiency**
- **Augmenting brain insulin levels and activity via intranasal administration may have therapeutic benefit**
- **Intranasal administration of regular insulin enhanced cognition, FDG PET, and affected CSF biomarkers in aMCI and AD** [Craft et al. 2012]

Intranasal Insulin to Normalize CNS Insulin Signaling



- **Insulin travels via bulk flow along rostral (olfactory) or caudal (trigeminal) perivascular channels; agents reach brain in minutes**
  [Thorne 2001]
- **Axonal transport via olfactory neurons, requires hours to reach brain**

Effects of Intranasal Insulin in MCI and AD



104 Adults
With aMCI/AD

INI (10 or 20 IU)
2x daily 4 months

Placebo

Baseline

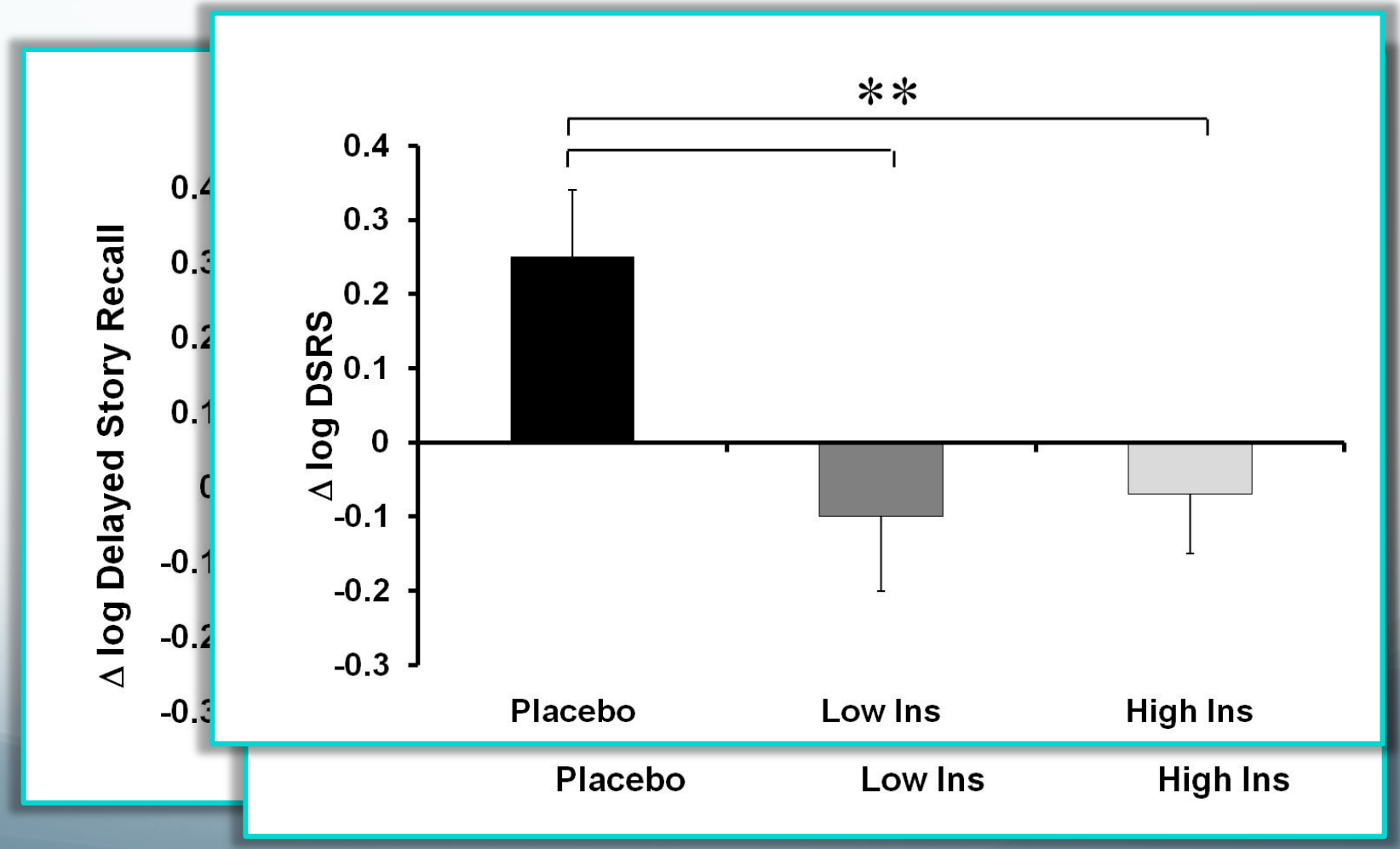
Month 4

Cognitive Function (ADAS-Cog,
Story Recall)
Function (DSRS)
FDG PET, CSF Biomarkers

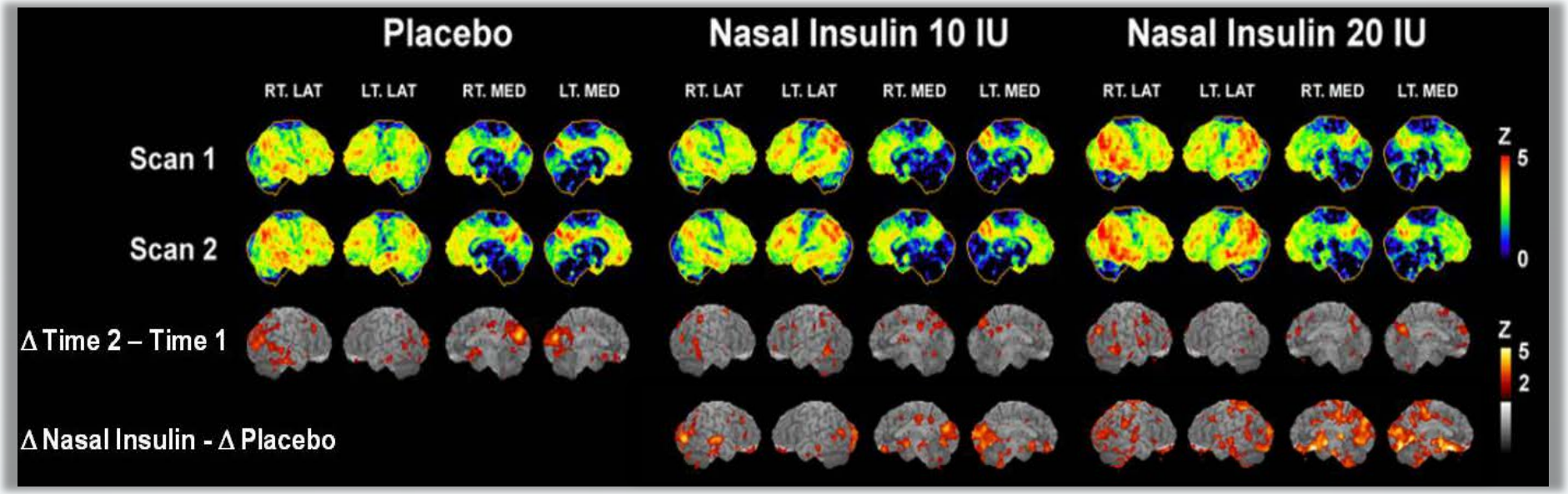
Craft et al. 2012

Results: Delayed Recall, Dementia Severity Rating Scale, ADAS-Cog

Change from Baseline to Month 4



Results: FDG-PET



Nasal Insulin 10 IU **Nasal Insulin 20 IU**

Δ Nasal Insulin – Δ Placebo
'Hot' colors reflect areas of greater hypometabolism for placebo

SNIFF PILOT STUDY: Safety and Compliance

- 4-month INI administration (10 or 20 IU bid vs. placebo) twice daily with ViaNase device
- **No treatment-related SAEs**
- Most common AEs: runny nose, dizziness

	Placebo	Low Insulin	High Insulin
Total AEs	27/56.7%	55*/72.2%	51+/68.4%
Dizziness	3/10%	3/8.3%	5/13.2%
Headache	1/3.3%	4/8.3%	2/5.3%
Nose bleed	0/0.0%	6/8.3%	3/2.6%
Rhinitis	1/3.3%	8/16.7%	4/7.9%
URI	2/6.7%	2/5.6%	1/2.6%
Fall	2/6.7%	1/2.8%	1/2.6%
Rash	2/6.7%	1/2.8%	2/2.6%
Other	16/46.7%	30/58.3%	33/60.5%

* Low Insulin Total AEs > Placebo, $p<0.05$
+High Insulin Total AEs > Placebo, $p<0.10$

Aim of Study

To examine the effects of **intranasally-administered insulin (INI)** on cognition, entorhinal cortex and hippocampal atrophy, and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment (aMCI) or mild Alzheimer's disease (AD)

Primary Aim

12 months of treatment with INI in aMCI and mild AD will improve performance compared to placebo on:

- Global cognition, ADAS-Cog 12 (Primary Outcome)

SECONDARY AIMS

1. INI improves performance on:
   - Memory composite (Paragraph Recall and FCSRT)
   - Executive function (Trail-Making Test)
   - Daily functioning (ADCS-ADL-MCI)

2. INI treatment :
   - reduces the rate of hippocampal and entorhinal atrophy
   - conduct exploratory analyses of other brain regions (MRI)

Secondary Aims cont'd

3. INI will favorably alter:
   - CSF Aβ
   - CSF Aβ/tau ratio
   - will modulate inflammatory markers

4. Whether the following predict treatment response
   - Baseline AD biomarker profile
   - APOE-ε4 allele carriage
   - Gender

SECONDARY AIMS cont'd

5. Safety and feasibility of INI treatment after 12 months

6. Whether further improvement occurs after 18 months of treatment

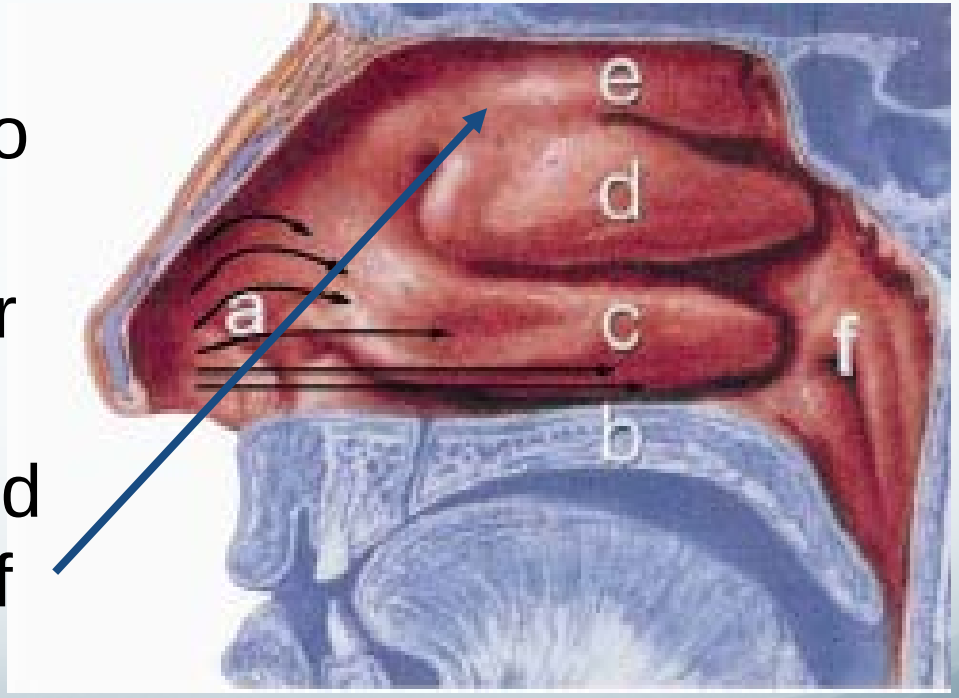
7. Safety profile after 18 months of treatment

8. **Feasibility and safety of using intranasal device for nose-to-brain delivery that will bypass the blood-brain-barrier**

Nasal Cavity Air Flow Patterns

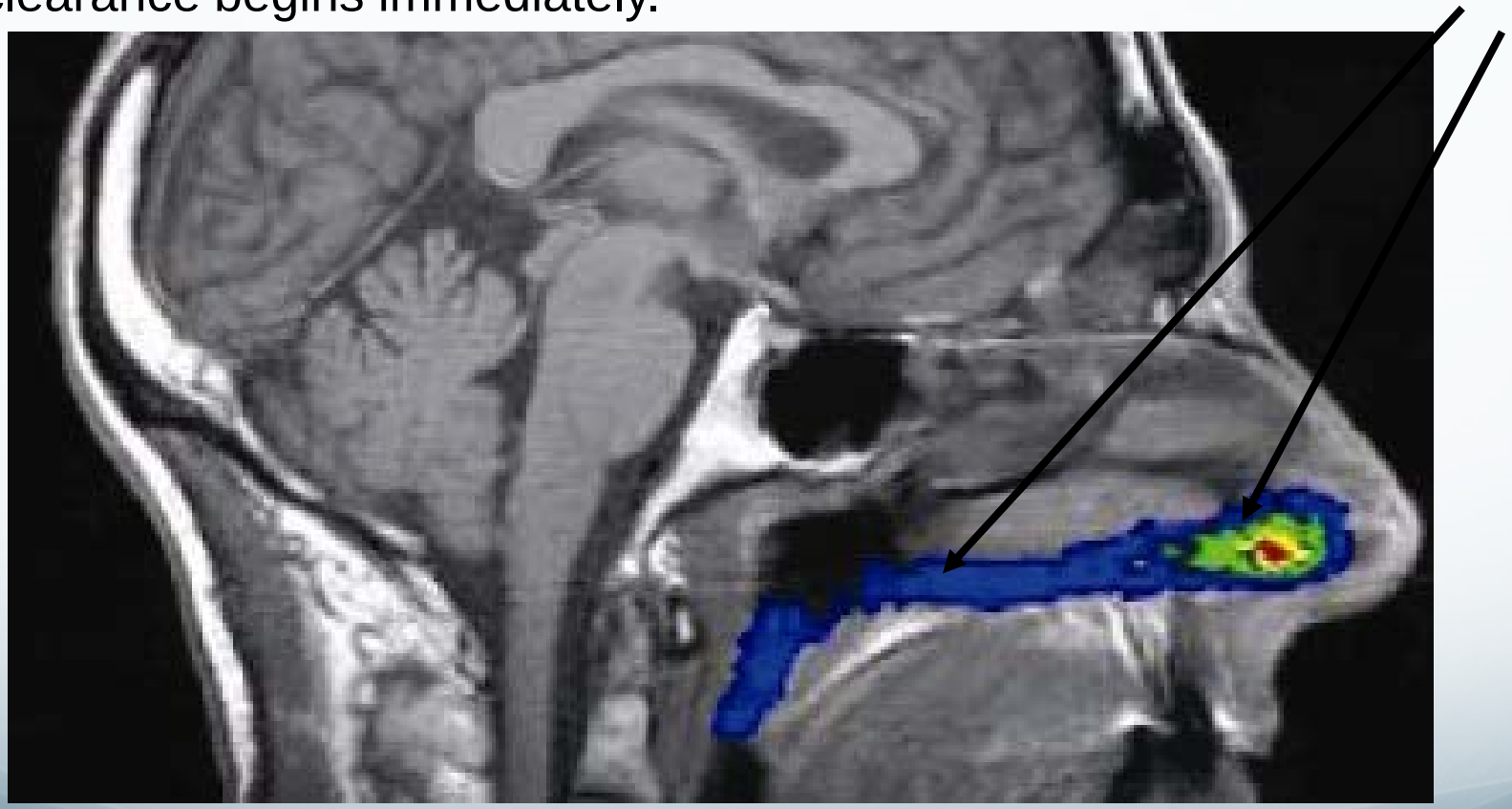
90% of the air flow that is inhaled through the nose follows the arrowed patterns

It is essential to cross this air stream in order to access the mucosa beyond the first 20% of nasal cavity



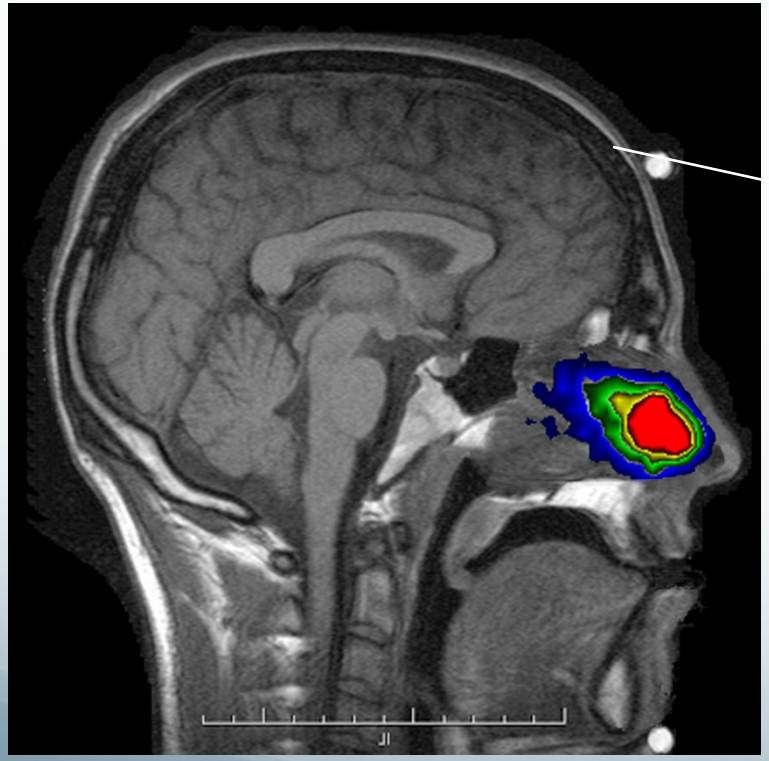
Typical Spray Bottle Deposition

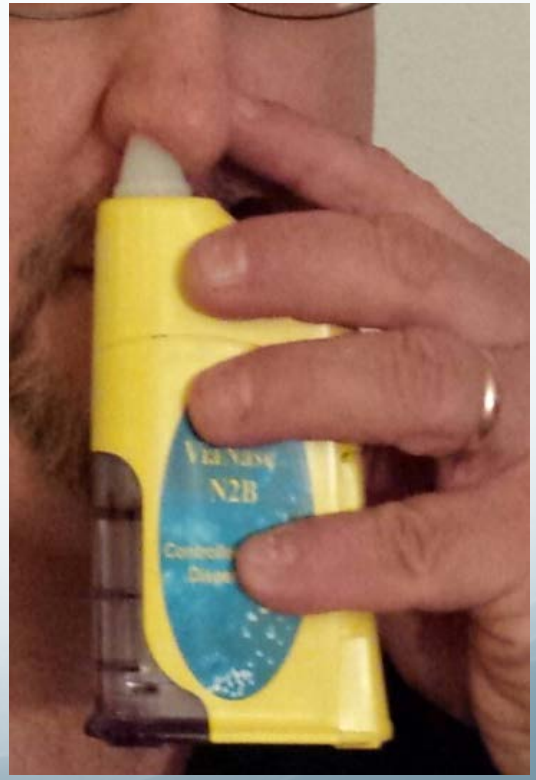
Large droplets in one dimensional flow impact the first obstruction and deposit. Gravity, air flow and clearance send 90% to the stomach. This clearance begins immediately.



ViaNase Device

Deposition with the ViaNase device is capable of crossing the air stream and negotiating the narrow pathways, depositing the entire dose throughout the nasal cavity, to the olfactory region and the paranasal sinuses





Study Design

- 240 participants (pts) with aMCI (50-60%) or AD
- 1:1 randomization (40 IU of daily INI:placebo)
- Placebo-controlled study for 12 months
- 6-month open-label period at end in which all participants will receive INI

Sites

- Banner Alzheimer's Institute
- Banner Sun Health Research
- Baylor College of Medicine
- Brigham & Women's Hospital
- Case Western Reserve University
- Georgetown University
- Howard University
- Indiana University
- Johns Hopkins University
- Mayo Clinic
- Jacksonville Mayo Clinic
- Oregon Health & Science Center
- Rhode Island Hospital
- Roper St. Francis Hospital
- Rush University Medical Center
- University of California, Irvine
- University of California, SD
- University of Kansas
- University of Kentucky
- University of Rochester
- University of South Florida
- University of Texas SWMC

Inclusion Criteria (selected)

1. Age 55 to 85 (inclusive)
2. Fluent in English or Spanish
3. Diagnosis of probable AD or aMCI
4. *MMSE ≥ 20 at screening; scores of 18 or 19 considered for minority or low education participants*
5. CDR 0.5-1 (inclusive) at screening
6. *For aMCI only: Screening Delayed WMS-R Logical Memory (Paragraph A only) ≤8 for ≥ years of education, ≤4 for 8-15, ≤2 for 0-7 years*
7. Modified Hachinski score ≤ 4

Inclusion Criteria (selected)

8. **A study partner able to attend most visits with direct participant contact > 2 days/week (min of 10 hrs/wk)**
9. **A study partner able to oversee or arrange assistance with study drug administration**
10. Stable medical condition for 3 months prior to screening
11. Stable medications for 4 weeks prior to the screening and baseline visits. *However, cholinesterase inhibitors and memantine must be stable for 12 weeks*

Exclusion Criteria (selected)

1. Use of **insulin or any other anti-diabetic medication at any time within 5 years of Screening visit. Continuous use of insulin or any other anti-diabetic medication for 1 year or longer during participant lifetime** (except prior SNIFF study participation)
2. Use of **nasal steroid or decongestant/antihistamine more than 2x week** and less than four days prior any cognitive testing

Schedule of Selected Outcomes/Procedures

Visit #	1	2	3	4	5	6	7	8
Visit Name/Month	Screen	Baseline	3	6	9	12	15*	18*
ADAS-cog12		X	X	X	X	X	X	X
MMSE	X			X		X		X
Memory Composite (Story Recall, FCSRT)		X		X		X		X
Trail-making Test (Part A & B)		X		X		X		X
ADCS-ADL-MCI		X		X		X		X
NPI		X		X		X		X
CDR	X			X		X		X
Treatment Blinding Questionnaire								X
Research Satisfaction Survey		X	X	X				X
Blood Draw	X	X		X		X		X
LP		X				X		
MRI	X[3]					X		

*Open Label visits

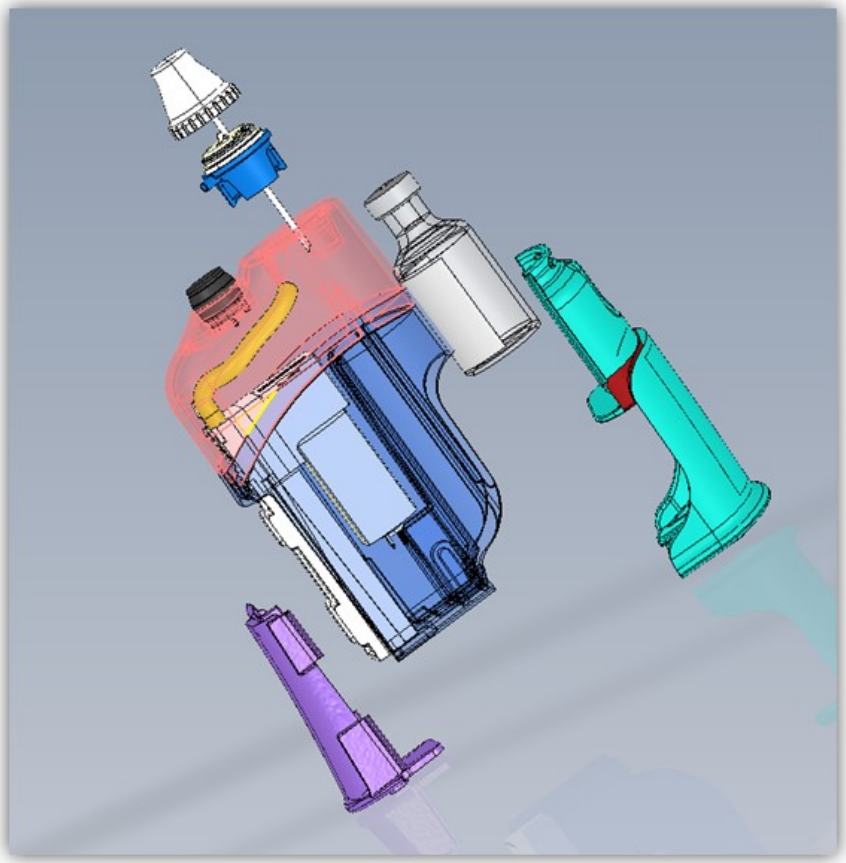
Progress to Date

Enrollment

- 72 individuals screened
- 28 participants randomized

Lessons Learned to Date

- Device Reliability Issues
  - Important study goal
  - Unanticipated needle breakage despite extensive lab testing due to rigid vial plug
  - Electronic issues on auto-time/battery interface
  - Both design features made to address initial investigator concerns
  - Recruitment paused
  - New, improved V2 device to be delivered 5/8, and screening resumes 6/1



- Sites, participants remain generally patient and enthusiastic despite inconvenience, recognize that this is important part of trial process

Other Plans to Address Device Issues

- **Under consideration: Device Repair Kit for participants**

Next Steps for Insulin-Related Therapies

- **Growing evidence supporting continued promise of insulin-based approaches for prevention and therapy**
- **Pilot studies in progress or planned for:**
  - **Combination therapy (ie., INI and anti-amyloid)**
  - **Direct delivery of insulin to brain via implanted pump/shunt**
  - **Nanoparticle insulin therapy**
  - **“Designer” insulins or related compounds (GLP-1) with enhanced favorable action, reduced unfavorable actions**

Primary Outcome Measure Schedule

ADAS-Cog12

- administered every 3 months from Baseline to Month 18

COGNITIVE EVALUATIONS SCHEDULE

- **MMSE**: at screen, 6 month, 12 month, 18 month visits
- **Memory composite** (Paragraph Recall & FCSRT): at baseline, 6 month, 12 month, 18 month visits
- **Trail-making Test** (Part A and B): at baseline, 6 month, 12 month, 18 month visits

Clinical & Functional Evaluation Schedule

- **CDR**: at screen, 6 month, 12 month, 18 month visits
- **ADCS-ADL-MCI**: at baseline, 6 month, 12 month, 18 month
- **NPI**: at baseline, 12 month

Imaging Schedule

- **MRI**: at Screen and Month 12 visits

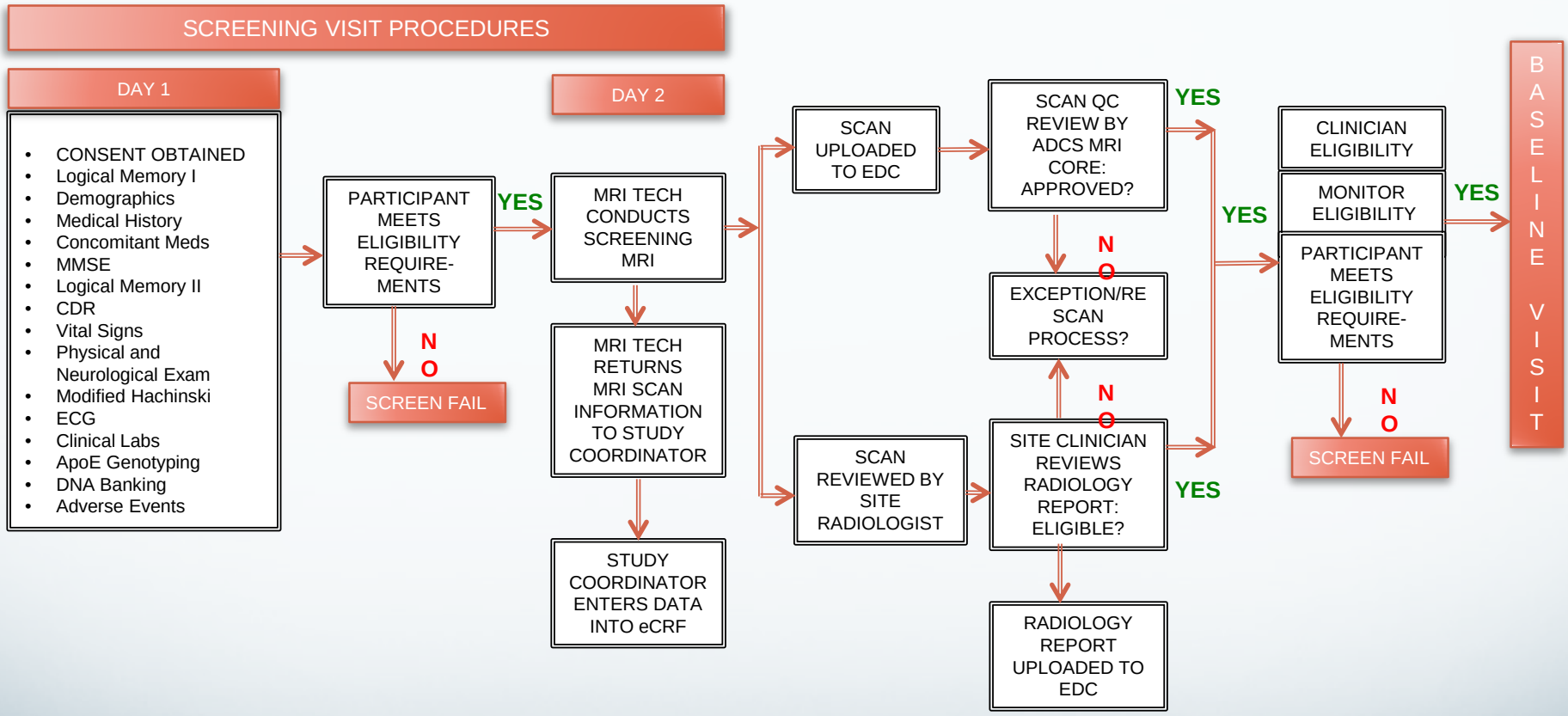
Biomarker Schedule

- **LP**: at Baseline and Month 12
- **Plasma, Serum and PBMCs**: at Baseline, M6, M12, M18

Safety Evaluations

- Safety MRI at Screening and M12
- Routine Safety labs at Screen, M6, M12, M18

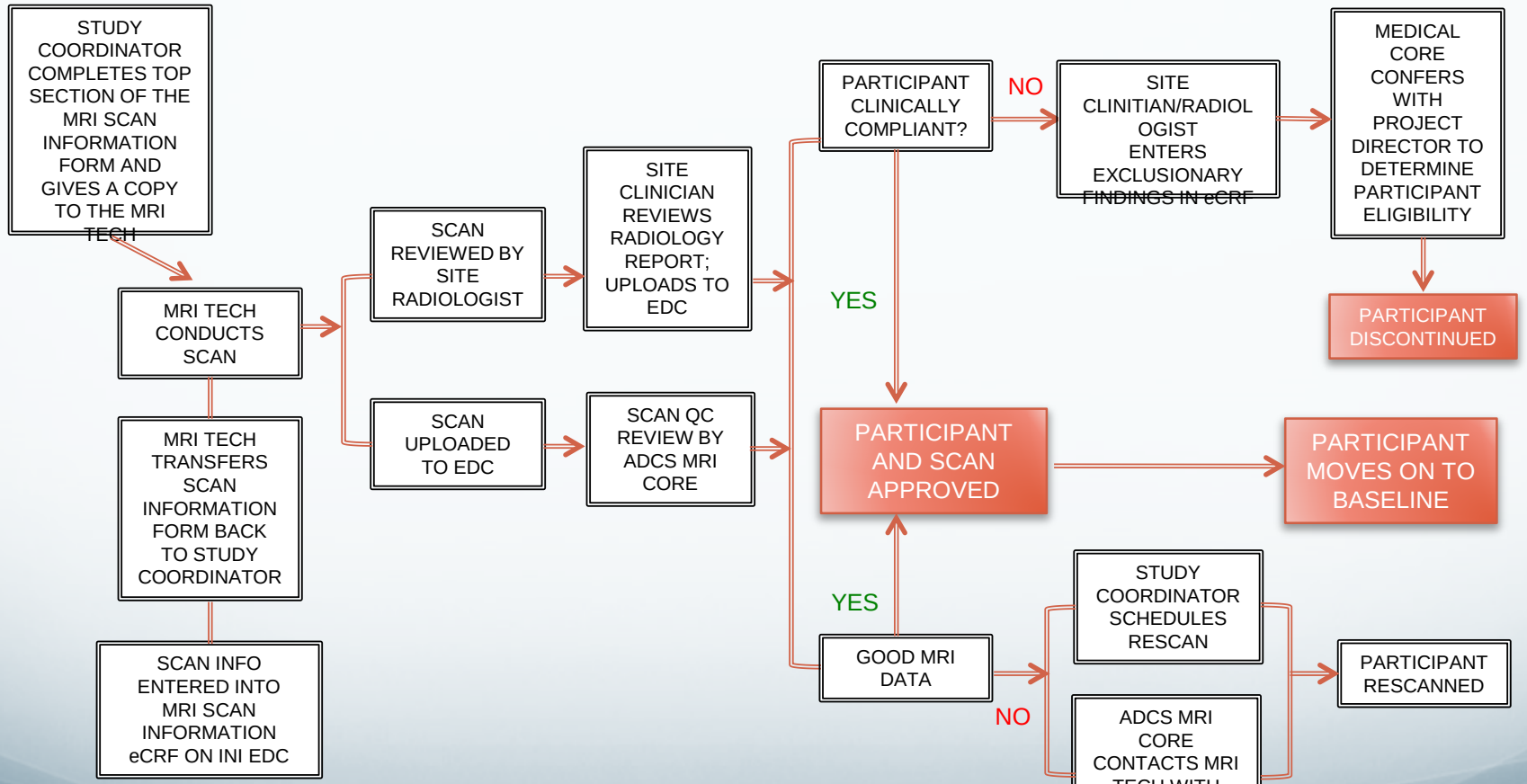
INI SCREENING PROCESS FLOWCHART



GENERAL GUIDELINES:

- The Table of Contents in the worksheet packet posted in the document repository reflects the order of assessments recommended by the Project Director
- **Informed Consent must be** obtained **prior** to initiating any screening **assessments**
- If a participant does not meet the **MMSE** inclusion criteria then do not proceed with the rest of the visit
- **Participants who do not meet inclusion/exclusion criteria and proceed to the MRI will not be reimbursed by ADCS**
- If a significant abnormality is seen in the MRI (e.g. hemispheric infarction), the participant will be excluded. Questionable abnormalities will be communicated to ADCS and the Project Director who will make a decision about participant eligibility
- **Upload all worksheets and reports, including laboratory report**

INI MRI DATAFLOW



INI SAMPLE VISIT SCHEDULE: SCREEN TO BASELINE

Baseline must be schedule within 2-4 weeks from the first day of screening

SCREENING

SCREENING - DAY 1

- Informed Consent
- Logical Memory I
- Demographics
- Medical History
- Concomitant Meds
- MMSE
- Logical Memory II
- CDR
- Vital Signs
- Physical and Neurological Exam
- Modified Hachinski
- ECG
- Clinical Labs
- ApoE Genotyping
- DNA Banking
- Adverse Events

Site Staff Checks Eligibility

SCREENING MRI - DAY 2

- **MRI** must occur after all Screening procedures have been completed but prior to initiating the Baseline visit
- Participants who do not meet inclusion and exclusion criteria and proceed with an MRI will not be reimbursed by ADCS

Monitor & Clinician Eligibility Approval

BASELINE

BASELINE - DAY 1

- ADAS-Cog 12
- Story Recall Immediate
- Trail-Making Test (Part A & B)
- ADCS-ADL-MCI
- Story Recall Delayed
- FCSRT Immediate
- NPI
- Research Satisfaction Survey
- FCSRT Delayed
- Vital Signs
- Nasal Exam
- Adverse Events
- Concomitant Meds
- INI Device and Study Drug administration Training

BASELINE - DAY 2

- Plasma Biomarker
- LP
- **Randomize Participant**
- **Dispense Study Drug**, Device and supplies, Study Diary and Participant Handbook

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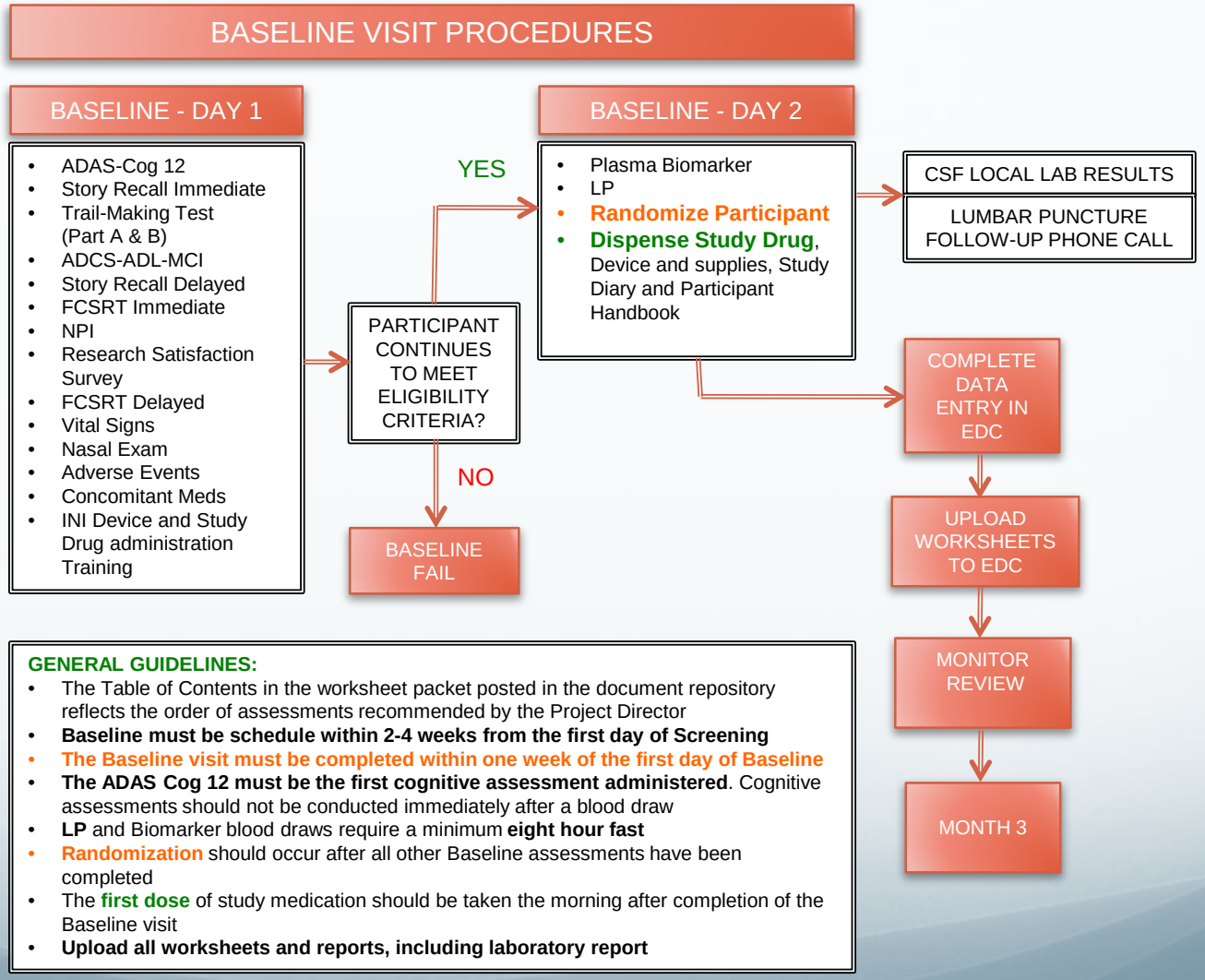
- If a participant does not meet the **MMSE** inclusion criteria then do not proceed with the rest of the visit
- **Participants who do not meet inclusion/exclusion criteria and proceed to the MRI will not be reimbursed by ADCS**
- **Upload all worksheets and reports, including laboratory report**
- LP and Biomarker blood draws require a minimum **eight hour fast**
- **ADAS Cog 12** must be the **first cognitive assessment** administered. Cognitive assessments should not be done immediately after a blood draw as this may affect the results
- **Randomization** should occur after all other Baseline assessments have been completed
- The **first dose** of study medication should be taken the morning after completion of the Baseline visits

THE BASELINE VISIT MUST BE COMPLETED WITHIN ONE WEEK OF THE FIRST DAY OF BASELINE

INI BASELINE FLOWCHART



PERSONNEL REQUIREMENTS

1. SITE PROTOCOL PRINCIPAL INVESTIGATOR
2. STUDY PHYSICIAN/SITE CLINICIAN
   - Accepted credentials: MD, DO, NP, APRN or PA-C
3. STUDY COORDINATOR
   - Can serve in multiple roles
4. UNBLINDED PHARMACIST
5. MRI CONTACT
6. INTERVIEWER/PSYCHOMETRIST
   - same person cannot administer both the ADAS-Cog and CDR for the same participant
7. REGULATORY
8. BILLING – REMITTANCE and STATEMENT

Study Drug

Insulin

Humulin® R U-100

- contains human insulin (rDNA origin) 100 units/mL, glycerin 16 mg/mL and metacresol 2.5 mg/mL, endogenous zinc (approximately 0.015 mg/100 units) and water for injection.

Placebo

Matching placebo

- Sterile Diluent

Study Drug Administration

- **Doses**: 2 daily 20 IU of INI (a total of 40 IU daily) or placebo. In BOTH nostrils
- Administered approximately 30-60 minutes after breakfast and dinner
- Keep device and study drug in refrigerator

Kurve®
TECHNOLOGY

Wake Forest Baptist Medical Center

IP Distribution Center

Study Drug: Compliance

Participants at each visit will return :

- all used and unused drug vials
- study diary (log drug intake twice daily)

Study Drug: Compliance

- Compliance metrics include:
  - Total number of doses taken over 3 months (per diary)
  - Number of used and unused returned vials
  - Visual inspection of vials (e.g., full, empty)
  - Interview of participant and study partner
- Compliance will be captured on EDC and IP Tracking Tool

Month _____ 20___ INI_____!

SNIFF Study
Participant Diary Notes

Please write here any comments on **missed doses, issues with spray, adverse reactions to the study drug** or other comments on the study drug administration.

DATE:	*COMMENT:*
DATE:	*COMMENT:*
DATE:	*COMMENT:*

!

For Study Coordinator Use - Dosing Summary:

Number of Doses Taken (Yes answers): _____

Number of Missed Doses (No answers): _____

Number of Unknown Doses (Blank answers): _____

# of Expected Doses (# days from start day to end day X 4 doses a day): _____

Compliance Formula:

$$\frac{\text{\# of Doses Taken}}{\text{\# of Expected Doses}} \times 100 = \text{\% Compliant}$$

Comments:

!

SNIFF STUDY MEDICATION DIARY

Baseline – Month 3

Start Date: __ __ / __ __ / __ __ __ __ **AM**
m m d d y y y y PM

End Date: __ __ / __ __ / __ __ __ __ **AM**
m m d d y y y y PM

- Note above the day and time of your first and last those
- Circle YES (Y) or NO (N) under RIGHT and LEFT nostril every morning (AM) and evening (PM) to note if you took the study medication
- Use spray about 30 min AFTER breakfast and 30 min dinner
- Keep the spray and the vials in the refrigerator
- Take spray out of the fridge about 30 min before using
- Rinse the nosepiece once a day under running water
- Throw away nosepiece and insert a new one once a month
- A vial will last about 2 weeks, insert another when empty
- Change researchable batteries at least once a week
- Return all used and unused vials of study medication at your next in-clinic study visit to the study coordinator

For questions contact your Study Coordinator at:

_____

DO NOT DISCARD VIALS!

Baseline-Month 3

Month _____ 20___ INI_____

DAY		RIGHT NOSTRIL	LEFT NOSTRIL		RIGHT NOSTRIL	LEFT NOSTRIL
1	AM	Y / N	Y / N	PM	Y / N	Y / N
2	AM	Y / N	Y / N	PM	Y / N	Y / N
3	AM	Y / N	Y / N	PM	Y / N	Y / N
4	AM	Y / N	Y / N	PM	Y / N	Y / N
5	AM	Y / N	Y / N	PM	Y / N	Y / N
6	AM	Y / N	Y / N	PM	Y / N	Y / N
7	AM	Y / N	Y / N	PM	Y / N	Y / N
8	AM	Y / N	Y / N	PM	Y / N	Y / N
9	AM	Y / N	Y / N	PM	Y / N	Y / N
10	AM	Y / N	Y / N	PM	Y / N	Y / N
11	AM	Y / N	Y / N	PM	Y / N	Y / N
12	AM	Y / N	Y / N	PM	Y / N	Y / N
13	AM	Y / N	Y / N	PM	Y / N	Y / N
14	AM	Y / N	Y / N	PM	Y / N	Y / N
15	AM	Y / N	Y / N	PM	Y / N	Y / N
16	AM	Y / N	Y / N	PM	Y / N	Y / N

DAY		RIGHT NOSTRIL	LEFT NOSTRIL		RIGHT NOSTRIL	LEFT NOSTRIL
17	AM	Y / N	Y / N	PM	Y / N	Y / N
18	AM	Y / N	Y / N	PM	Y / N	Y / N
19	AM	Y / N	Y / N	PM	Y / N	Y / N
20	AM	Y / N	Y / N	PM	Y / N	Y / N
21	AM	Y / N	Y / N	PM	Y / N	Y / N
22	AM	Y / N	Y / N	PM	Y / N	Y / N
23	AM	Y / N	Y / N	PM	Y / N	Y / N
24	AM	Y / N	Y / N	PM	Y / N	Y / N
25	AM	Y / N	Y / N	PM	Y / N	Y / N
26	AM	Y / N	Y / N	PM	Y / N	Y / N
27	AM	Y / N	Y / N	PM	Y / N	Y / N
28	AM	Y / N	Y / N	PM	Y / N	Y / N
29	AM	Y / N	Y / N	PM	Y / N	Y / N
30	AM	Y / N	Y / N	PM	Y / N	Y / N
31	AM	Y / N	Y / N	PM	Y / N	Y / N

Totals	AM	__ / __	__ / __	PM	__ / __	__ / __

Totals	AM	__ / __	__ / __	PM	__ / __	__ / __

Study Drug Management

IP Tracking Tool

Study drug management tool on the INI Data Portal

- To track:
  - Study Drug Inventory
  - Drug Shipment
  - Drug Accountability and Destruction
  - Compliance
- **Users:**
  - Wake Central Pharmacy
  - Site Unblinded Pharmacy
  - Study Coordinators
  - Monitors