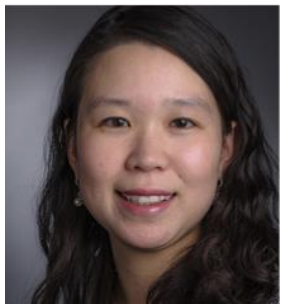
Monday March 7, 2022

NIDUS Mentoring Webinar: PILOT AWARDS: Developing a competitive LOI / Submitting a successful application

Michael Avidan, MBBCh, FCA SA



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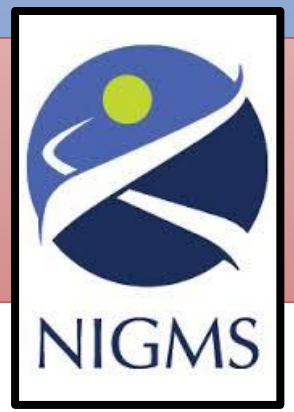
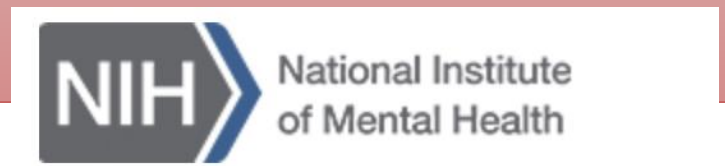
Acknowledgements

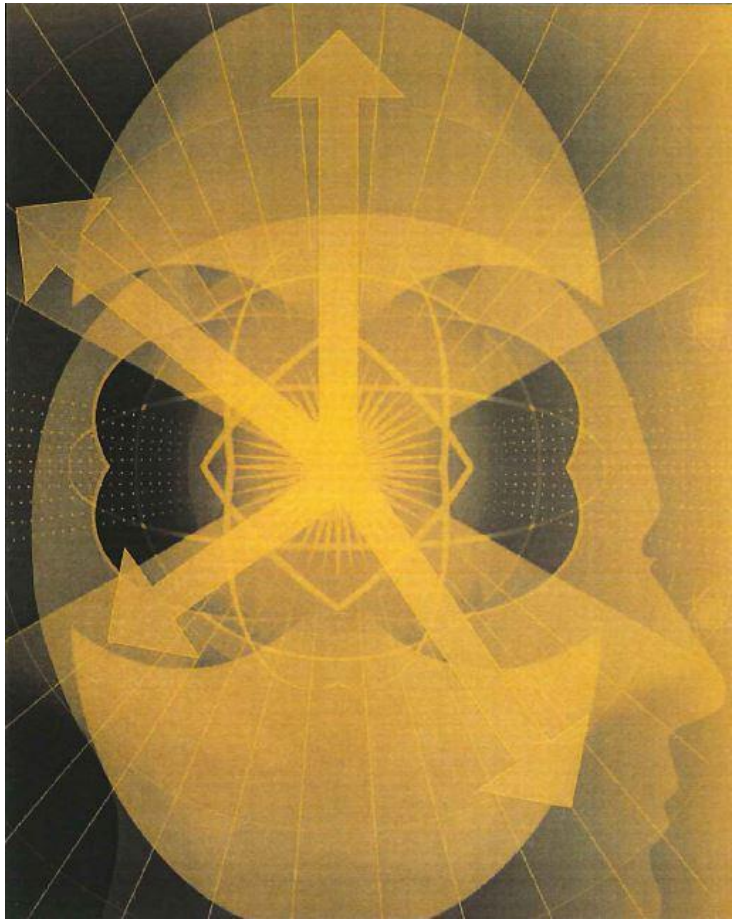
I have no conflicts of interest to declare.





Objectives

- On Pilot and Feasibility Studies
- How to develop strong NIDUS II LOIs
- How to develop strong NIDUS II pilot / feasibility grant applications
- An example of a NIDUS funded pilot / feasibility grant
- Your questions about your current pilot award application or the NIDUS II pilot / feasibility LOI/application process

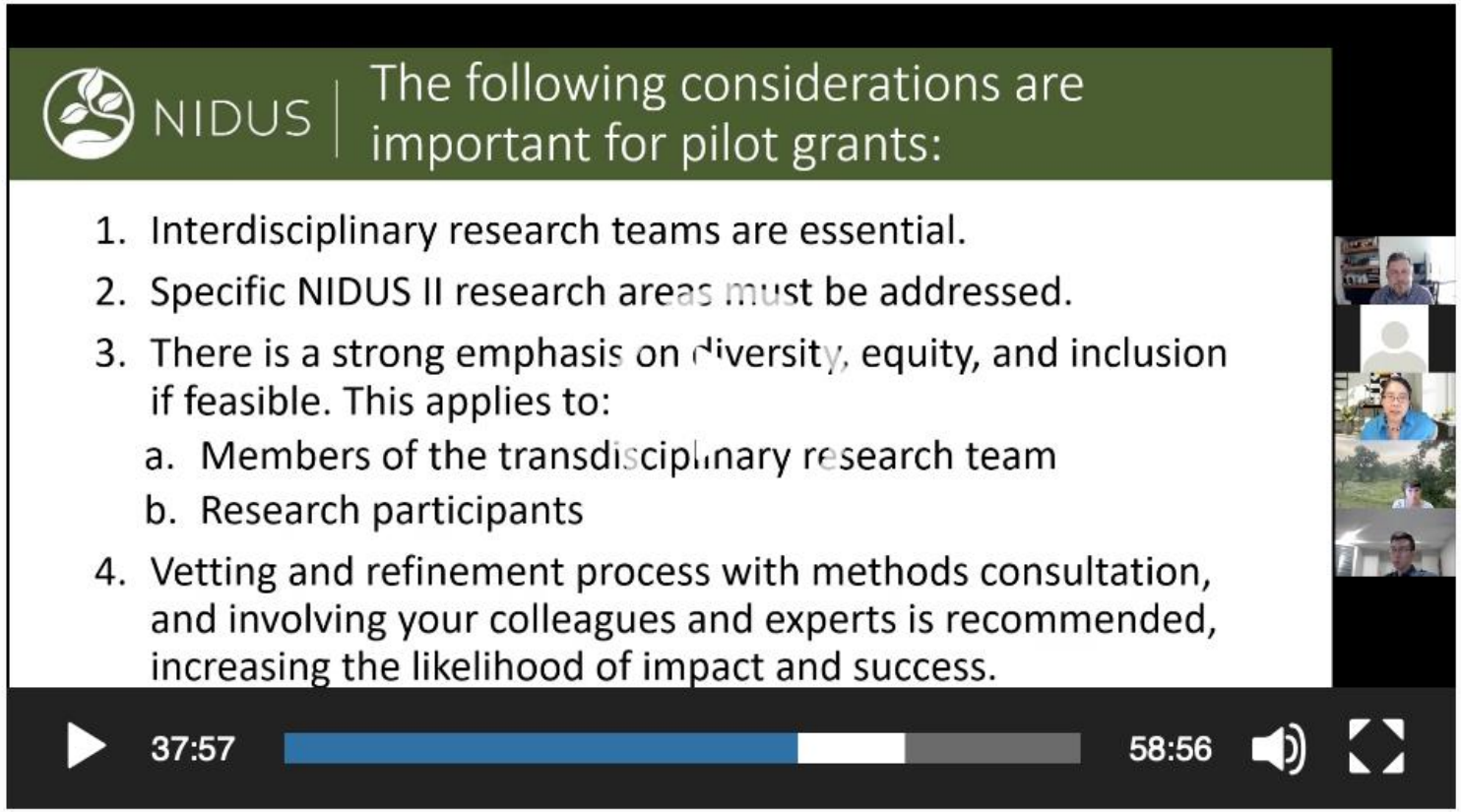


Disclaimer

We cannot cover everything, but we can give you **a few key pieces of advice and point you in the right direction**.

We will not spend much time on information that has already been presented in prior NIDUS webinars.

NIDUS II Pilot Grant Information Session (09/09/21)



Hear all about the NIDUS Pilot Grants and NIDUS Resources by viewing this video.

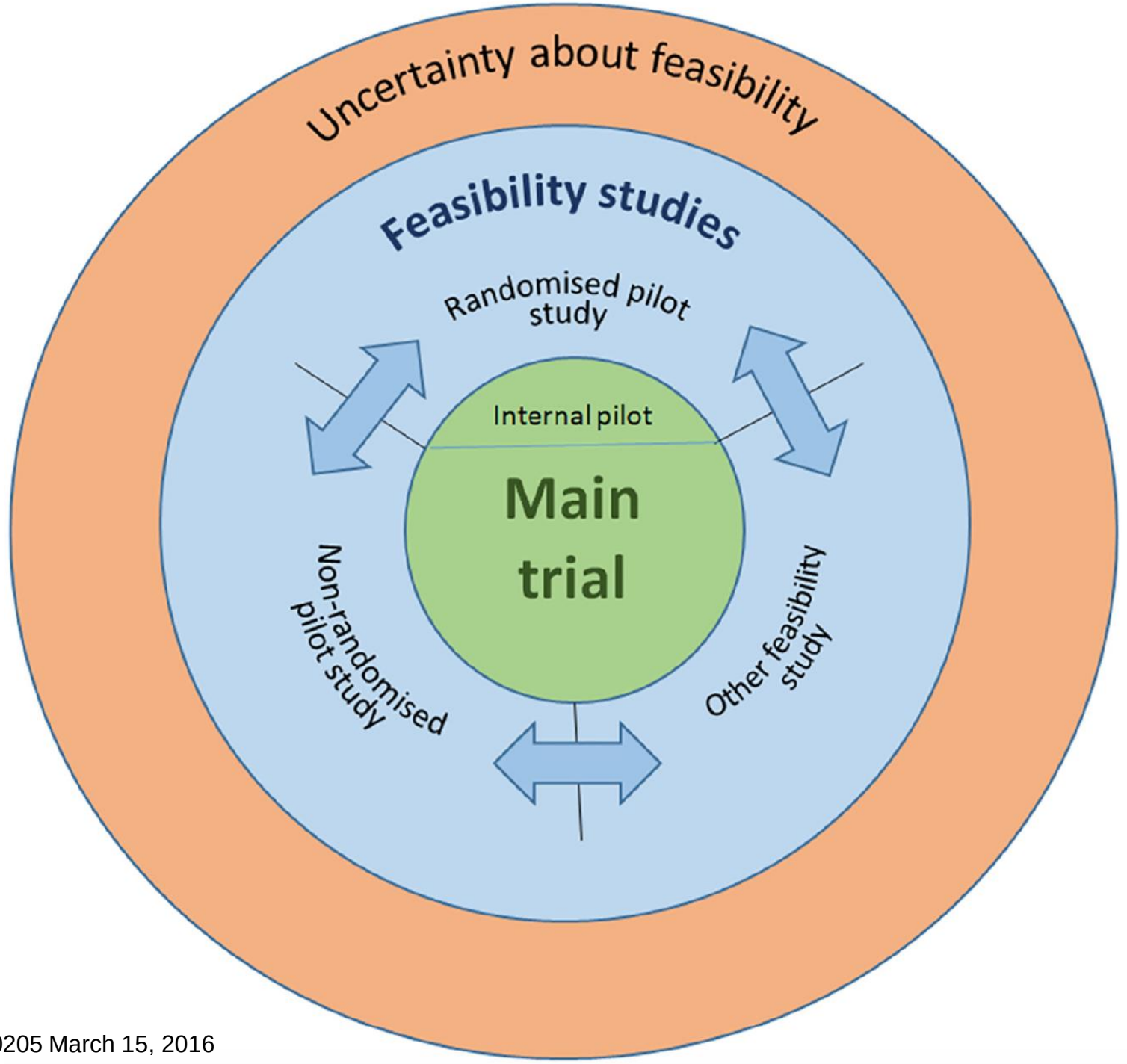
NIDUS | Pilot and Feasibility Studies

What are the distinguishing features?

Neither addresses efficacy or effectiveness!

- **<u>Pilot studies are a subset of feasibility studies</u>**, rather than the two being mutually exclusive.
- A feasibility study asks whether something can be done, should we proceed with it, and if so, how.
- A pilot study asks the same questions but also has a specific design feature: in a pilot study a future study, or part of a future study, is conducted on a smaller scale.

PLOS ONE | DOI:10.1371/journal.pone.0150205 March 15, 2016



PLOS ONE | DOI:10.1371/journal.pone.0150205 March 15, 2016

Areas of Focus in Feasibility Studies

- Acceptability
- Demand
- Implementation
- Practicality
- Adaptation
- Integration
- Expansion
- Preliminary data
- Limited efficacy

Bowen DJ et al. Am J Prev Med 2009;36(5):452–457

Lancaster and Thabane *Pilot and Feasibility Studies* (2019) 5:114
https://doi.org/10.1186/s40814-019-0499-1

Pilot and Feasibility Studies

EDITORIAL Open Access

Guidelines for reporting non-randomised pilot and feasibility studies

Gillian A. Lancaster* and Lehana Thabane

Table 1 Main types of non-randomised feasibility studies submitted to the journal, where to find guidance and published examples

Type of study	Equator website checklists and other helpful guidance	Published examples
Intervention development	TIDieR http://www.equator-network.org/reporting-guidelines/tidier/ Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers (O'Cathain et al): https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-015-0026-y	Thematic series on intervention development available at: https://www.biomedcentral.com/collections/interventiondevelopment
Patient-Reported Outcome Measures (PROMS) development	CONSORT PRO (adapt alongside CONSORT extension to pilot trials) http://www.equator-network.org/reporting-guidelines/consort-pro/ COSMIN User Manual (comprehensive reference, useful risk of bias tool) https://cosmin.nl/wp-content/uploads/COSMIN-syst-review-for-PROMs-manual_version-1_feb-2018.pdf	Thematic series on pilot and feasibility testing of patient-reported outcome measures available at: https://www.biomedcentral.com/collections/pilotfeasibilityPROMs
Piloting several components of the trial	CONSORT extension to pilot trials (ignoring items not applicable) http://www.equator-network.org/reporting-guidelines/consort-2010-statement-extension-to-randomised-pilot-and-feasibility-trials/	Aging, Community and Health—Community Partnership Program before-after study [25]: https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-016-0063-1 POWeR-RN non-randomised study with wait-list control [26] https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-017-0122-2#Sec16

Implementation of research findings	CONSORT extension to pilot trials (ignoring items not applicable) http://www.equator-network.org/reporting-guidelines/consort-2010-statement-extension-to-randomised-pilot-and-feasibility-trials/ RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework for evaluating interventions http://www.re-aim.org/ Please note that when applying RE-AIM to pilot and feasibility studies, 'potential effectiveness' only should be addressed.	Thematic series on implementation science and practice forthcoming at: https://www.biomedcentral.com/collections/implementationscience-pilotstudies GLA:D® Back before-after study [28]: https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-019-0448-z GenerationPMTO before-after study [29] https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-019-0476-8
Feasibility studies in preparation for a cohort or other large scale study	STROBE (ignoring items not applicable) http://www.equator-network.org/reporting-guidelines/strobe/ CONSORT extension to pilot trials (ignoring items not applicable) http://www.equator-network.org/reporting-guidelines/consort-2010-statement-extension-to-randomised-pilot-and-feasibility-trials/ • Ensure there is adequate explanation as to why the study is a feasibility study, and state clear feasibility objectives • Ensure a formal sample size calculation is reported if hypothesis testing is carried out	Community-based paediatric respiratory infection surveillance cohort study [31]: https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-018-0371-8 Prognosis of patients with apparent treatment-resistant hypertension [32]: https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-018-0232-5
Feasibility studies that test preliminary hypotheses of association	STROBE (ignoring items not applicable) http://www.equator-network.org/reporting-guidelines/strobe/ CONSORT extension to pilot trials (ignoring items not applicable) http://www.equator-network.org/reporting-guidelines/consort-2010-statement-extension-to-randomised-pilot-and-feasibility-trials/ • Ensure there is adequate explanation as to why the study is a feasibility study, and state clear feasibility objectives • Ensure a formal sample size calculation is reported if hypothesis testing is carried out	Is cognitive function in delirium associated with EEG frequency band connectivity (case-control study) [33]? https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-018-0388-z Are foetus mouth movements associated with sound stimulation in the womb [34]? https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-016-0053-3

ELSEVIER

Check for updates

Journal of Clinical Epidemiology

Journal of Clinical Epidemiology 138 (2021) 102–114

ORIGINAL ARTICLE

Pilot and feasibility studies for pragmatic trials have unique considerations and areas of uncertainty

Claire L Chan[a,1], Monica Taljaard[b,c,1,*], Gillian A Lancaster[d], Jamie C Brehaut[b,c], Sandra M Eldridge[a]

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Accepted 29 June 2021; Available online 3 July 2021

Domain	Highly pragmatic approach	Highly explanatory approach
Intervention development	Develop an intervention that, if shown to be effective, would be ready and acceptable for implementation in usual care	Develop an intervention that exerts its effects through a postulated causal pathway with less consideration to its complexity and acceptability in clinical practice
Research Ethics	Adopt waived or altered forms of consent to minimize additional burden over usual care procedures	Adopt traditional full informed consent procedures
Eligibility	Include participants in the trial that are similar to those who would receive the intervention if it were part of usual care	Include a subsample of the target population more likely to show a beneficial effect
Recruitment	Recruit participants with no more effort than would be used in usual care to engage with patients	Recruit participants using more intensive recruitment strategies set up for research purposes
Setting	Include a range of centers and settings similar to where the results are intended to apply	Perform the trial in a setting with conditions intended to maximize the potential of demonstrating efficacy
Organization	Use no more resources, provider expertise, or organizational structure than those available in usual practice	Employ specialized resources, such as trained professionals to deliver the intervention
Flexibility of delivery	Deliver the intervention with the same flexibility that is anticipated in usual care, often leaving the details of how to implement the intervention up to the providers	Ensure providers comply with a highly standardized protocol for delivery of the intervention
Flexibility of adherence	Allow participants to engage with the intervention with the same variability that is anticipated in usual care, monitoring and encouraging adherence no more than would take place in usual care	Put measures in place to ensure participants adhere to the intervention as much as possible
Follow-up	Data collection and follow-up guided by usual care practices	Follow participants intensively, through more frequent and longer visits
Primary outcome	Select a primary outcome that is directly relevant to participants	Select a primary outcome on which the intervention is expected to have a direct effect

CONSORT Extension

Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	
	2b	Specific objectives or research questions for pilot trial	
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
	4c	How participants were identified and consented	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	
Sample size	7a	Rationale for numbers in the pilot trial	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the pilot trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
	19a	If relevant, other important unintended consequences	
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	
Protocol	24	Where the pilot trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	
	26	Ethical approval or approval by research review committee, confirmed with reference number	

Using NIDUS Resources to Advance your Research

Guide to NIDUS II Resources https://deliriumnetwork.org/

NIDUS Resource	Website links	Description
General on NIDUS resources	Informational video: https://deliriumnetwork.org/wp-content/uploads/2021/09/zoom_0.mp4	Informational Video from NIDUS "Happy Hour"
NIDUS Measurement Information Cards	https://deliriumnetwork.org/measurement/delirium-info-cards/	Information on over 40 Delirium Measurement Tools
NIDUS Measurement Harmonization tools (2)	https://deliriumnetwork.org/measurement/delirium-identification-measures-crosswalk-tool/ https://deliriumnetwork.org/measurement/delirium-severity-crosswalk-tool/	Crosswalk links and software to harmonize delirium measurements across studies
NIDUS Research Hub	Hub: https://deliriumnetwork.org/delirium-research-hub/ Informational video: https://www.youtube.com/watch?v=RpFUfdeUuKM&t=23s	Many uses—find collaborators, find studies, find data or specimen resources

Guide to NIDUS II Resources https://deliriumnetwork.org/

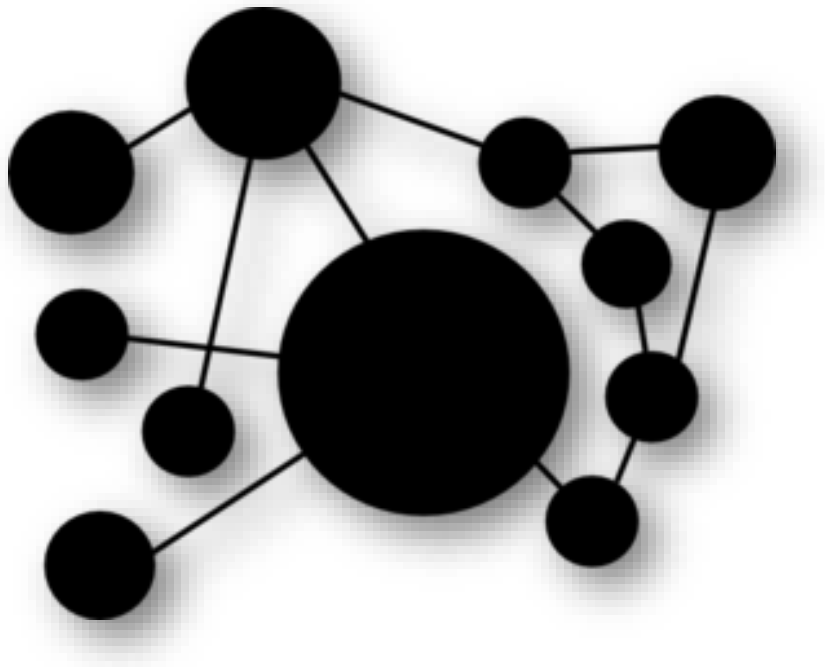
NIDUS Resource	Website links	Description
NIDUS Collaboration Communication Site	https://deliriumnetwork.org/delirium-research-hub/collaboration-communication-site/	Reach out to potential collaborators
NIDUS Delirium Bibliography	https://deliriumnetwork.org/bibliography/	>4000 indexed articles on delirium
Attend NIDUS Webinars	https://deliriumnetwork.org/career-development/webinars/	Announced regularly on website—sign up to get announcements
Attend NIDUS Bootcamp	https://deliriumnetwork.org/career-development/nidus-bootcamp/	Intensive Delirium Research Training by experts in the field
Tours of the NIDUS Resources	Email: Nidus@hsl.harvard.edu Phone: (617) 971-5390 Twitter: @nidus_delirium Facebook: NIDUSDelirium	Schedule a time to get a tour of the NIDUS website and resources

Goal of NIDUS II Pilot Studies

These Awards are designed to support studies related to delirium that provide key preliminary data, exploratory or proof-of-concept pilot work, feasibility studies, or secondary analyses that define a clear pathway to future large-scale studies and grants

In NIDUS II Priority Areas….

NIDUS II Priority Areas



1. **Inter-Relationship of Delirium and ADRD**: studies on risk factors, pathophysiology, and treatment.
2. **Measurement of delirium**: Harmonization and refinement of measurement, with a goal towards unified assessment.
3. **Pathophysiology**: Biomarker and mechanistic studies to advance our understanding and identify therapeutic targets.
4. **Clinical Trials--Intervention Development** studies for future clinical trials, especially of **treatments** for delirium.

Developing a Feasibility / Pilot Study

Suggestions for steps to developing a pilot study:

- Assemble a team – Utilize NIDUS Collaboration Communication site
- Develop a protocol -- NIDUS Delirium Bibliography
- Data sources-- NIDUS Research Hub
- Data Collection/Synthesis of data—NIDUS Measurement Core
- Develop the pilot—Collaborative Working Group!!

Keys to Success

- **Don’t be overly ambitious** in your aims.
- Do **be specific** in what you hope to accomplish.
- Consider the **scoring criteria**.
- Be explicit regarding the **next steps**, including large funding proposal.
- Use **figures or infographics** creatively.
- Use **simple language** and avoid abbreviations.

- Understand what **type of feasibility** study you are proposing.
- Set clear and realistic **deliverables** for the feasibility study.
- Do focus on **feasibility outcomes**.
- Do use **NIDUS II resources**.
- Take full advantage of NIDUS II **Methods Consultations**.
- Do demonstrate your **commitment to delirium** research.

The Design of the Feasibility Phase 30 patient Trial

Randomization is like a coin toss

PROPOFOL TIVA

Randomization of Patients Undergoing Surgery with General Anesthesia

INHALED VOLATILE

30 Patients Across 2 Centers

Recovery After Surgery

Daily Wearable Signals

EFFECTIVENESS OUTCOMES AND BENEFITS

measured between postoperative day 0 and 90

Quality of Recovery

Functional Status

Delirium

Activity

SAFETY OUTCOMES AND SIDE EFFECTS

measured between postoperative day 0 and 90

Awareness with Recall

Kidney Injury

Respiratory Failure

Mortality

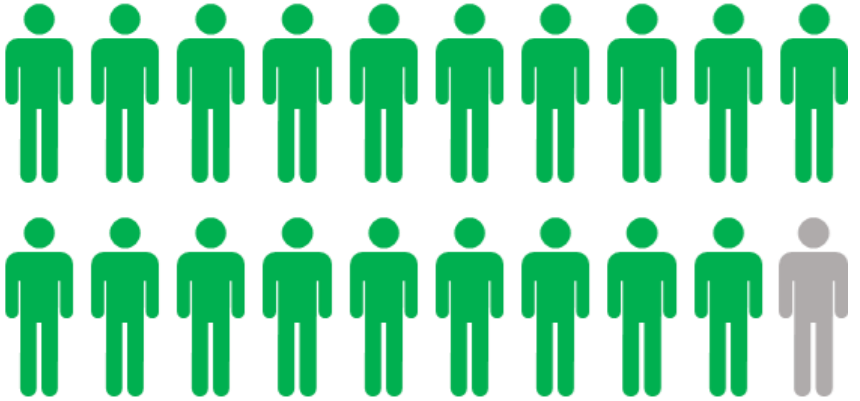
THRIVE

What could success look like in a THRIVE feasibility trial?

Primary Aim 1:
Enough patients will accept the invitation to take part

> 3 of 10, (30%) agree to participate

Primary Aim 2:
Both TIVA (intravenous anesthesia) and inhaled anesthesia (breathed into the lungs) can be given successfully



> 19 of 20 (95%) for both protocols

NIDUS II Collaborative Awards

Letter of Intent for pilot grants (were due 11/15/2021)

Ten $1,000 collaborative grants were awarded

Methods consultations were awarded to refine your pilot grant application

Requirements for NIDUS Pilot Proposals

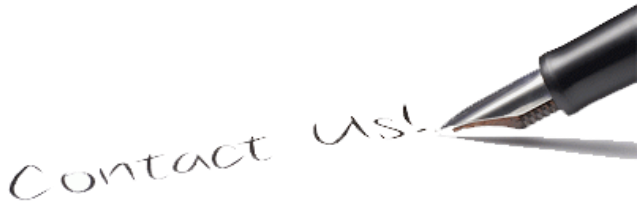
$40,000: two awards to be awarded in 2022

1. Required: Approved pre-application (letter of intent) and NIDUS II methods consultation. A NIDUS II Collaborative award is NOT required to apply for a NIDUS II pilot grant.
2. Must complete 4-page brief NIH style proposal
3. Priority to projects relevant to the NIDUS II priority areas and lay the groundwork for future collaborative grants and papers.
4. Utilize our NIDUS Cores and resources to accomplish the work.
5. Involve 3-6 investigators from multiple disciplines.
6. Preference for projects that involve multiple sites and include junior investigator(s).

Review Criteria for NIDUS Pilot Grants

1. Scored on NIH review criteria: Significance, Investigators, Innovation, Approach, Environment
2. Relevance to aging and delirium research in a priority area
3. Feasibility/likelihood that the proposed study can be completed within one year
4. Use of NIDUS Core resources (e.g., Measurement/Harmonization Core, Research Hub)
5. Involvement of multiple disciplines
6. Involvement of a junior investigator
7. Commitment to diversity, equity, and inclusion
8. Likelihood that the proposed study will lead to a future large grant proposal and/or major scientific publication that will help to advance delirium treatment

We're available to help build connections



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Follow NIDUS online! Twitter: @nidus_delirium Facebook: NIDUSDelirium

Open Discussion