

How to write a research proposal? By Susan Gau, M.D., Ph.D.

如何撰寫臨床研究計畫書

How to Write a Research Proposal?



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Outlines



Why do we write grants and do research?

- **Love science**
- **Career development & promotion**
- **Personal Objectives**
- **Employer or expectation from peers, teams, or mentors**
- **Fame, incentives, and financial reward**
- **Improving clinical skill/knowledge and patient care**
- **Mentoring followers**
- **Domestic and international impact**
- **Others**



Medical Writing: The Facts and the Myths

- **Myth:** “Until I have my ideas clearly organized in my head, I shouldn’t start writing.”
- **Fact:** The best way to clarify thinking is to start writing. Research shows the act of writing helps to clarify and organize thinking and to generate ideas.

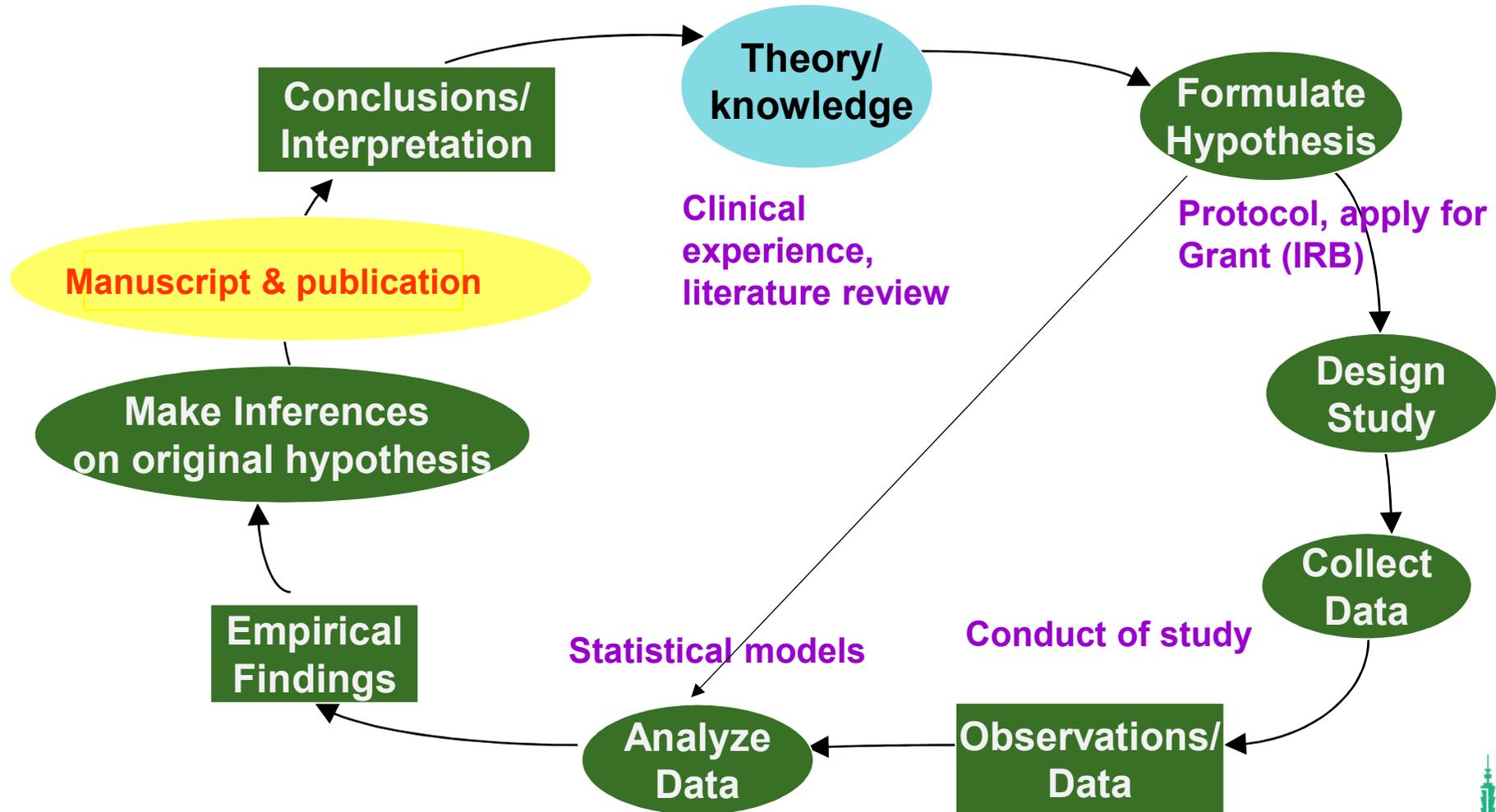
- **Myth:** “I’m not going to stay in academics. I’m going into a private practice. I won’t be writing much at all.”
- **Fact:** All medical professionals need to write.



Outlines



Conceptualization of the Scientific Method



Qualities of Good Scientific Writing

- **Reader (Reviewer-based)**
- **Purposeful**
- **Clear**
- **Concise**
- **Correct**
- **Simple**
- **No invented words, No jargon**
- **Few, if any, abbreviations**



Ways to Improve Your Writing

- **Practice.** If possible, set aside some time each day to write. What should you write about? **Anything.** Write up a case report, your impressions of a patient, a letter to the editor of a journal, a review, and finally, write an original article. What you write in not as important as **that you write.** This exercise will improve not only your writing but also help to **refine your thinking.**
- **Model.** To model your writing after good writing. Read papers or grants with good writing as models. For examples: NEJM, Nature series, Science, JAMA, Lancet, and top journals in your fields. As you become more aware of your own writing, you'll begin to differentiate between writing that is easy to read and writing that is painful to read.
- **Good writing.** takes **time, patience, and practice**—but it's worth it. Keep in mind that sometimes the only thing that others see of you is what you put on paper. If your writing is disorganized, illogical, and illiterate, that may be the impression readers and reviewers will have of you.



Mentorship: A good mentor

- **Set a good (successful) model**
- **Defining good research questions**
- **Writing**
- **Apply for grants**
- **Networking in Taiwan and worldwide**
- **Financial and manpower support as you get started**

How to Start: Ideas/questions

- **#Research Questions**
(important, interesting, novel, significant...)
 - Your knowledge from clinical work, literature review, previous studies
 - Your colleagues and advisors
 - Support from environment and funding resource
 - Global or local direction (顯學)

Grants

Types of Grants:

- Project vs, CDG
- Basic vs. Clinical Research
- Individual vs. Program project
- Hypothesis-driven vs. Hypothesis generating research

Founding Sources:

- Government (MOST, NHRI, MOE, MOHW, CDC etc.)
- NTU/NTUH
- Industries
- Foundations/donation
- International Institutes

Clinical Research

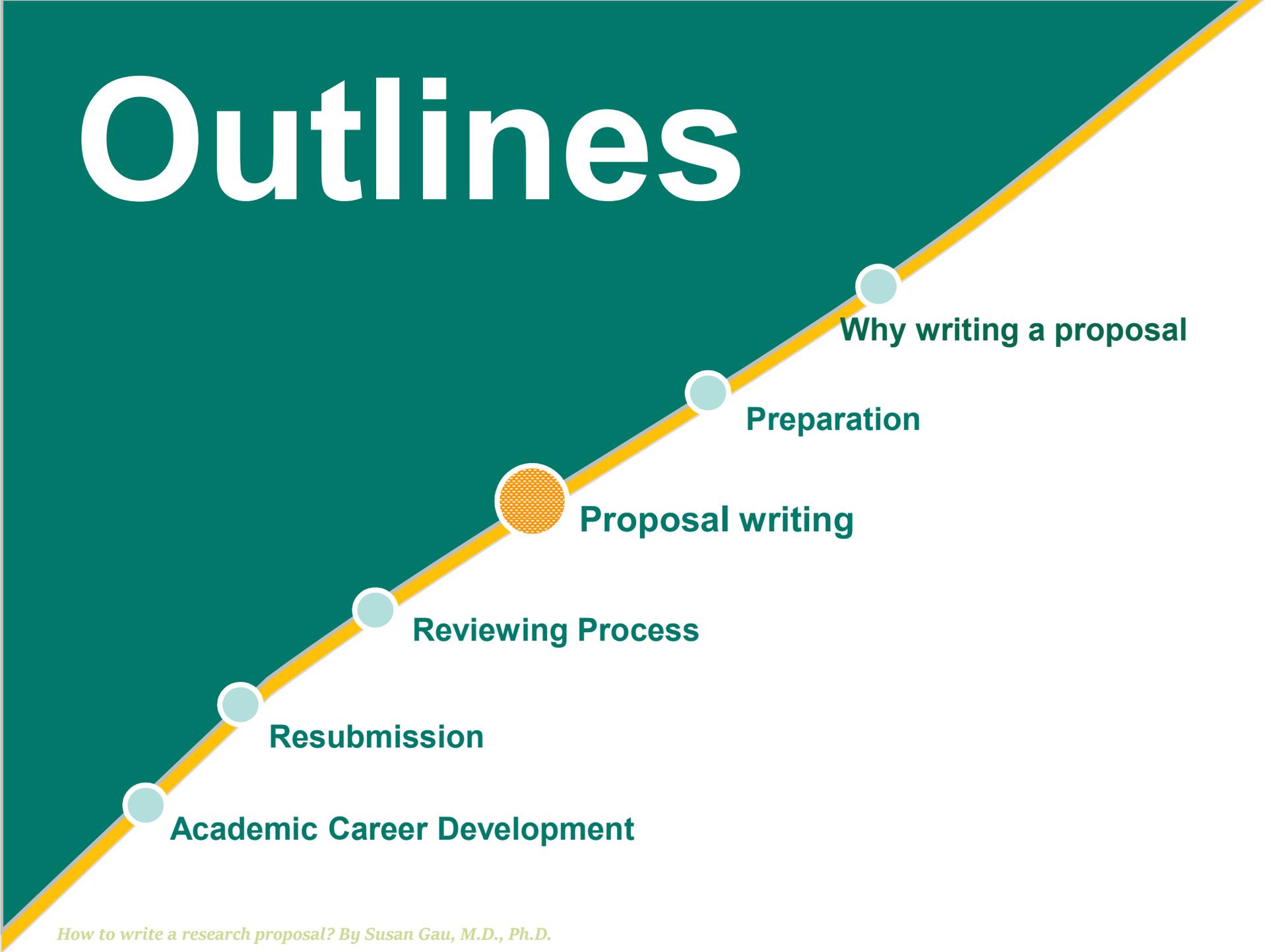
- **Important Disease Topics (Autism, ADHD, Dementia, COVID-19, etc)**
- **Studying:**
 - **Pathogenesis mechanism**
 - **Validity of Diagnoses**
 - **Treatment**
 - **Follow-up, prognosis**

ADHD/ASD



SUSAN GAU'S LAB

Outlines



Why writing a proposal

Preparation

Proposal writing

Reviewing Process

Resubmission

Academic Career Development

Write a Research Proposal

- **What:** Specific Aims & Hypothesis
- **Why:** Background & Significance, Rationale
- **How:** Methods/Study Design
- **When:** Time table
- **Who:** Personnel (PI, co-PI, RA, GS), record, preliminary results
- **Where:** Environment, Institutional Support
- **How much:** Budget, Expense



Abstract of the Grant proposal

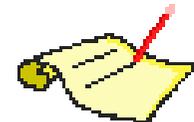
- Most widely read part of the grant
- Used to direct grant for review
- Read first -- critical first impressions may be formed from the abstract
- Read by all Study Section Members
- Write it last



Abstract of the Grant proposal

✓ Study scheme

- ✓ Abstract of study design
 - ✓ Specific aims
 - ✓ Study hypothesis
 - ✓ Background
 - ✓ Methods: Sample, Procedures, Measures & instruments.....
 - ✓ Anticipated results
 - ✓ Contribution
 - ✓ Importance
- ✓ ... should be in brief but clearly!



背景：

自閉症類群疾患(autism spectrum disorder, ASD)及注意力不足過動症(attention-deficit hyperactivity disorder, ADHD)皆為常見(盛行率：ASD, 1%；ADHD, 3-10%)、具基因與臨床上極度複雜性的早發於兒童期且持續至成人期的神經發展疾患，造成個人、家庭及社會極大的衝擊。即使國內外眾多的臨床、神經認知/影像及基因研究，截至目前為止，ASD 和 ADHD 的致病機轉仍不清楚，缺乏有效的檢測、預防和生物性治療(ADHD 雖有藥物，30%無效；ASD 尚無藥物)，越來越多的研究指出此兩者共病存在，部分症狀、神經心理學、腦結構有重疊現象以及可能相似的潛在性致病機轉，然而極少的研究同時詳細地探討此兩種疾病；近年來，代謝體和微生物體在神經精神疾患的角色逐漸受到重視；另外，本計畫主持人在不同時期投入 ADHD 和 ASD 神經認知/影像/基因研究，雖然對這兩個疾病的了解較多，但其機轉和基因變異仍不明，綜合以上論點，進行多面向前瞻性的腦-腸軸線的整合性研究以代謝為主軸，針對患有 ADHD 和 ASD 的兒童，以找出此二疾病共同及獨特的基因-微環境交互作用機制是極具迫切且重要的。

目的：

1. 對照於典型發展兒童，於4-12歲的兒童找出影響ASD和ADHD的腸內菌叢微生物體、神經心理認知、神經影像(結構、功能、代謝物)的早期環境暴露因子(例如：母體及於產前至產後、幼兒時的環境暴露因子等等)。
2. 透過兩次時間點的重複測量比較臨床症狀、神經心理學、神經影像學、腸內菌叢微生物體、血液代謝體、代謝核磁共振之特有的生物標的物及微環境特徵並且同時考慮當前之食物、腸胃道症狀和生活方式的影響。
3. 探索2-4年長期追蹤下，ASD、ADHD、TDC之兒童的症狀、神經心理學、神經代謝影像學、腸內菌叢微生物體和血液代謝體等各項生物標的之變化(追蹤時-第一次)、穩定性與變化之的交互作用。
4. 找出環境(周產、飲食、生活型態、家庭、學校、社區)和個人(行為、微生物體、代謝體和結構性腦造影)因素，可以前瞻性地預測ADHD和ASD的神經認知/腦功能及社會心理表現。

方法：

此五年期的多面向前瞻性研究，預計將於前三年收集90位ASD、90位ADHD和90位典型發展對照組(年齡4-12歲)之臨床症狀/診斷、社會心理功能、認知神經心理學(CANTAB)、大腦代謝(MRS)和結構功能性造影(T1, T2, DTI, 靜息-fMRI)、代謝體(血液)及腸微生物體(糞便)資料，並且先完成第一階段的實驗分析，整合多面向資料，進行橫斷面相關性分析並進行分析找出腸-腦軸線的相互調節路徑及關鍵性的生化分子。第四五年(約2-4年後)追蹤所有三組受試者，重複所有測量，預計能追蹤約204位受試者(每組各68位)完成重複評估。第二階段的分析，重複第一階段分析，並增加多面向資料的縱貫性分析及路徑分析。

顯著性及預期之成果：

本計畫是第一個同時納入ASD及ADHD兩個最常見的神經發展疾患和典型發展對照組，以同樣的方法學建立多面向資料庫(環境、臨床、行為認知、腦影像、代謝體、微生物體、基因生物學)，以整合性地探討神經發展疾患多面向代謝體之間關係、腸內菌之生態菌叢演變、以及分析

ADHD/ASD



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Research Plan

- **Specific Aims (1page)**
- **Background and Significance (2-3 pages)**
- **Preliminary Studies**
- **Previous and Current Studies of the PI**
- **Research Design and Methods**
- **Anticipated Results**
- **Others (Human Subjects.....)**
- **References**



Specific Aims

- Three levels of Generality
- Broad long term goals
- Specific research aims
- Hypotheses or questions generated by the specific aims
- Optional: Brief rationale
 - Deflects incorrect inferences



Specific Aims

- **General Statement**
 - General public health importance
 - Prevention
 - Treatment/cure/rehabilitation/recovery
 - Description/ epidemiology
 - Etiology /association
- **Broader context also applies to**
 - Population under study
 - Risk factors of interest



Specific Aims

- Followed, typically, by more specifically delineated risk factors (independent variables) and disease outcomes (dependent variable)
- Brief description of data analysis strategies (optional)
- **Specific hypotheses**
 - Primary Aims
 - Secondary Aims



Background and Significance

- Briefly sketch the background to the present proposal
- Critically evaluate existing knowledge
- Specifically identify the gaps that the project is intended to fill.
- State concisely the importance of the research described in this application by relating the specific aims to the broad long-term objectives and to health relevance.



Background and Significance

DO:

- Cite relevant research of study section members
- Explain the clinical and/or public health importance of the proposed research
- Be focused, selective, concise, clear, scientific, unbiased, respectful.



Literature Review

- Determine major concepts and list in descending order of importance or in terms of logical presentation
- Prepare outline with major concepts as headings and list articles that relate
- Create **subheadings** as needed
- **Summarize** studies on same subtopics
- Introductory paragraph saying **what** will be presented, in **what** order, and **why**
- Summary **statements** for subtopics
- Summary paragraphs for major topic study
- Concluding paragraph typing it all together



Literature Review

- Establish what has been said to this point on the proposed topic
- **BE PERSUASIVE**
- Proposed hypotheses are sound
- Methods of inquiry are correct
- Point out gaps in literature
- Convey your mastery of the topic



Preliminary Studies

- To support feasibility of the proposed methodology:
 - To ensure that assumptions made are supported
 - To test study instrument

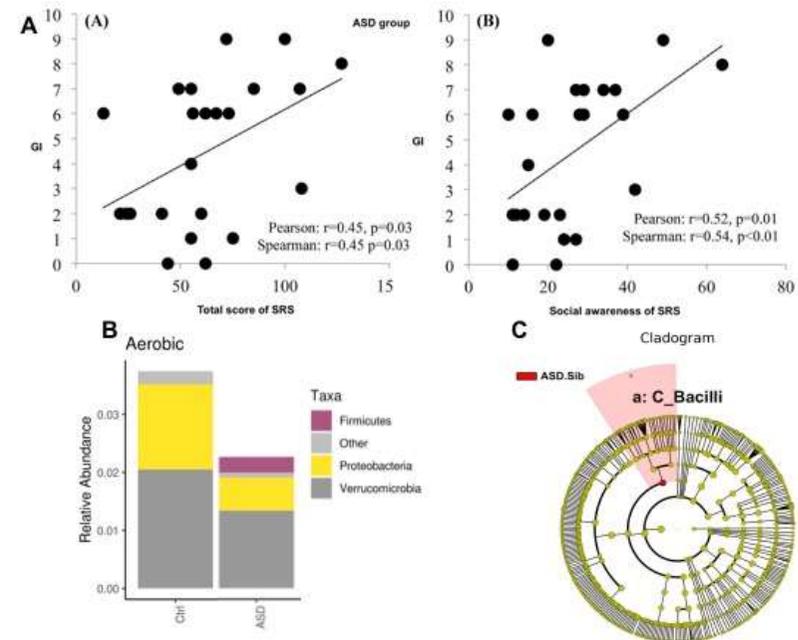


FIG 2. Preliminary results of microbiota compositions between two groups. (A) Correlation between GI symptoms' severity and autism behaviors. (B) The distribution of Aerobics in ASD and TDC. (C) The cladogram tree plot.



Previous and Current Studies of the PI

- **How the other studies may help establish the feasibility and importance of the new proposal**
- **Advantage of preliminary studies pertinent on new application of the new proposal**
- **Competence of PI**



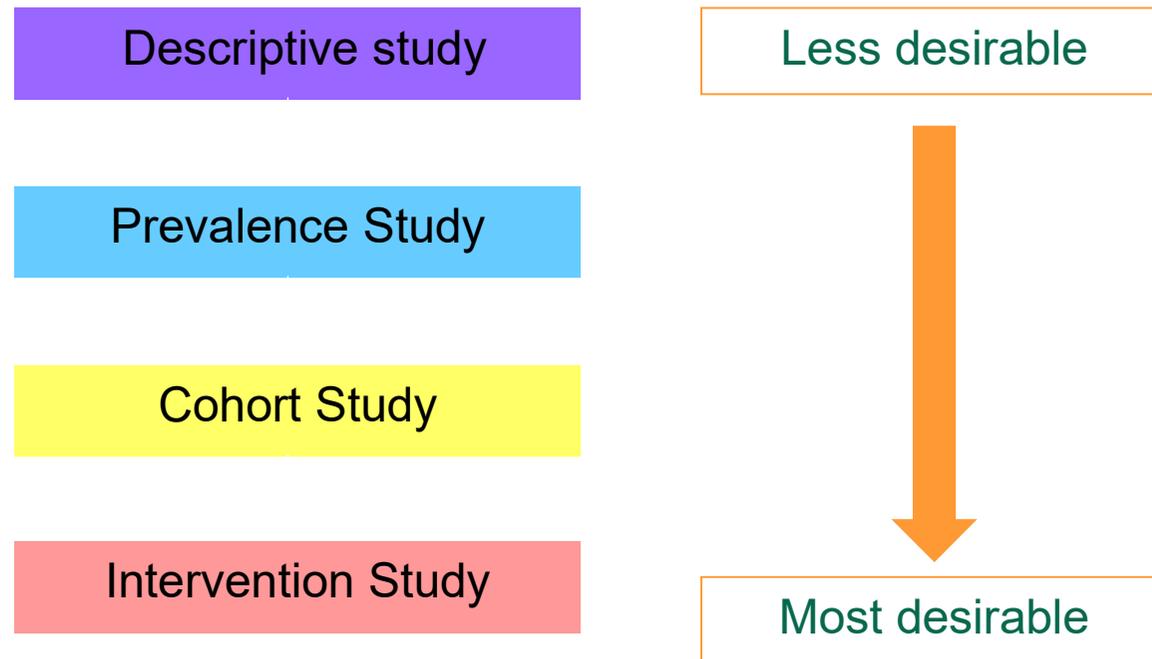
Study Hypothesis

- **Original hypothesis**
 - not tested in previous studies
 - needs to be supported by some other evidence
 - e.g., data on animals, indirect evidence from other studies
 - be biologically plausible
 - be consistent with theory
 - e.g., dose-response relationship
 - have public health importance
 - best if factor is modifiable and/or outcome is highly prevalent or has serious consequences



Study Hypothesis

- Hypothesis already tested in previous studies
 - most common
 - Move from one design to another design



Study Hypothesis

- **Hypothesis already tested in literature**
 - **Replicate findings when previous studies have limitations**
 - e.g., small sample size, unaccounted confounders
 - **Replicate findings in other subgroups of population**
 - e.g., elderly, women, minorities, children
 - **Replicate findings for a different outcome**
 - **Find “explanatory factors” for previously established associations**



Examples of Hypotheses

- **Pregnant women who smoked are at increased risk of pregnancy complications, including intrauterine growth retardation (IUGR), preterm delivery and preeclampsia, than women who don't smoke**
- **The risk of having low birth weight baby, offspring with developmental delay and attention-deficit increases with increases quantity of tobacco mother smoke during pregnancy**
- **Children with ADHD are more likely to develop conduct disorder and impaired peer relationship at adolescence**



Level of Subject Selection

Level of Selection

Main Exclusions

Target population

Subjects not assessed

Subjects assessed and found not eligible

Source population

Subjects not classified because of inadequate data

Eligible subjects

Exclusions because of death, inability to cooperate, administrative issues, confidentiality, voluntary non-response...(do not enter study)

Study participants

Failure to complete study requirements, missing data (do not complete study)



Level of Subject Selection

Target population(s) the population(s) to which the results can be applied

Direction of selection of subject

Direction of application of subject

Source population the population(s), defined in general terms and enumerated if possible, from which eligible subjects are drawn

Selection

Application

Eligible population the population(s) of subjects eligible for inclusion in the study should be defined precisely and counted

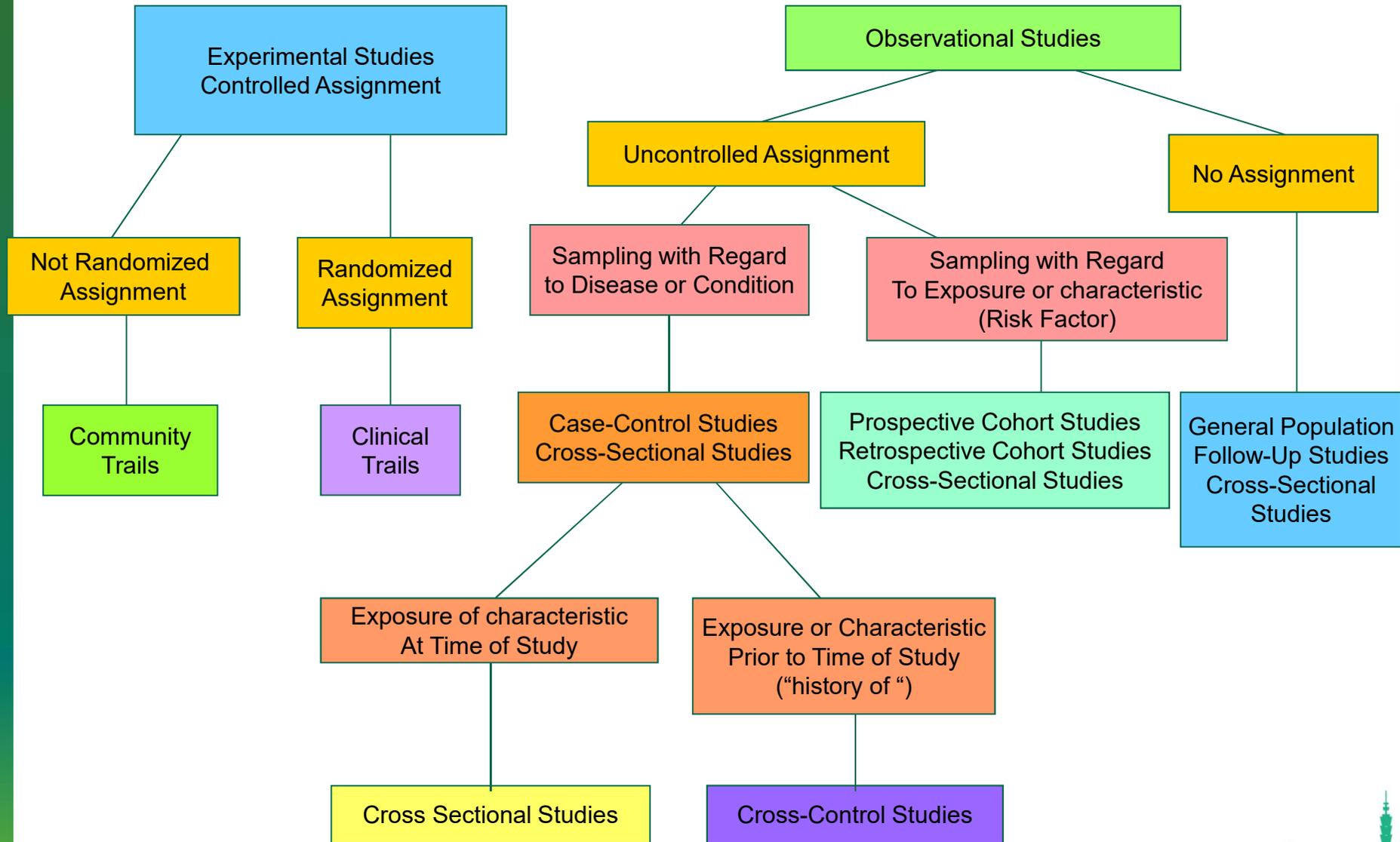
Selection

Application

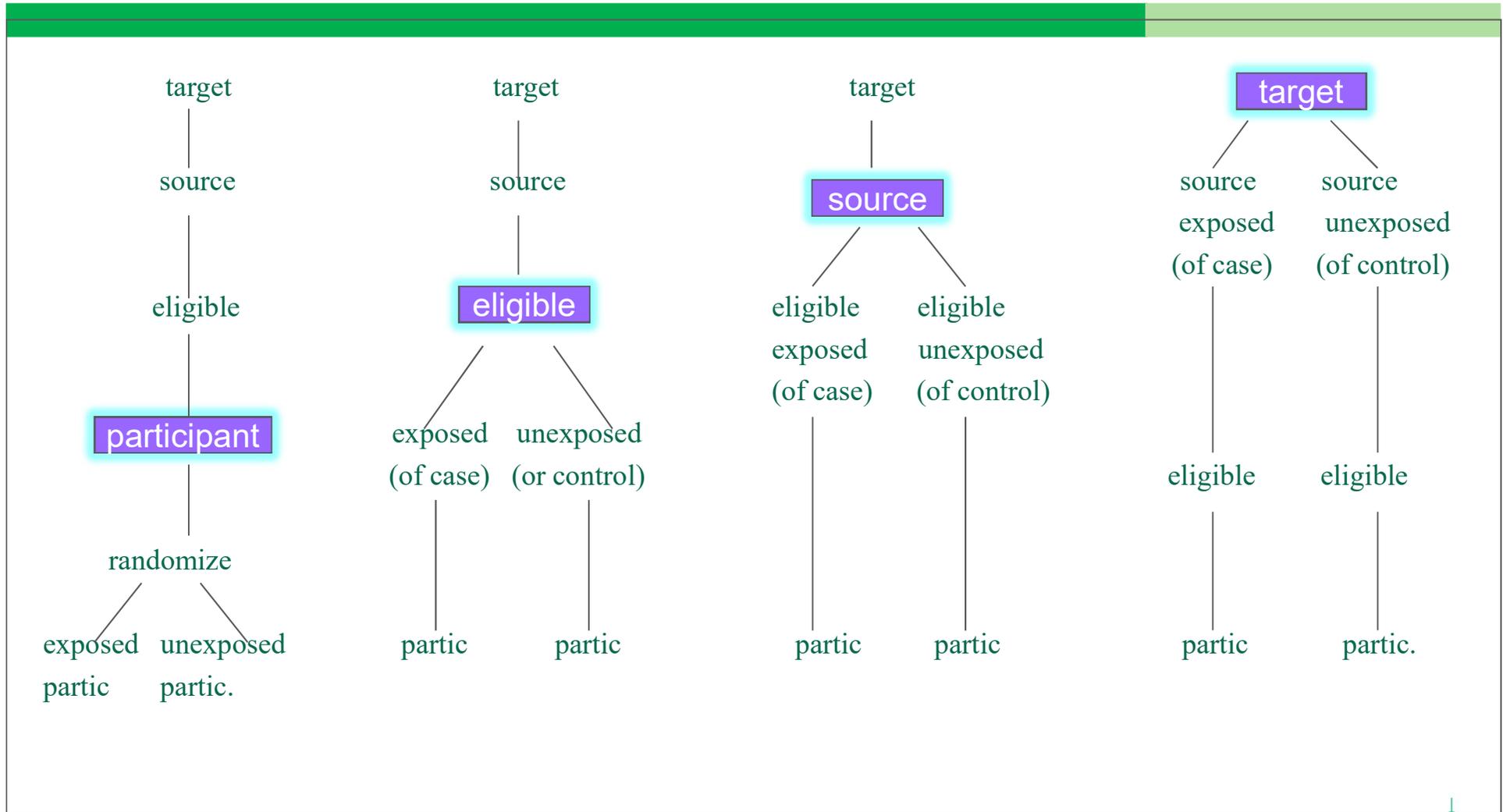
Study participants those individuals who contribute data to the study the results apply directly only to these subjects



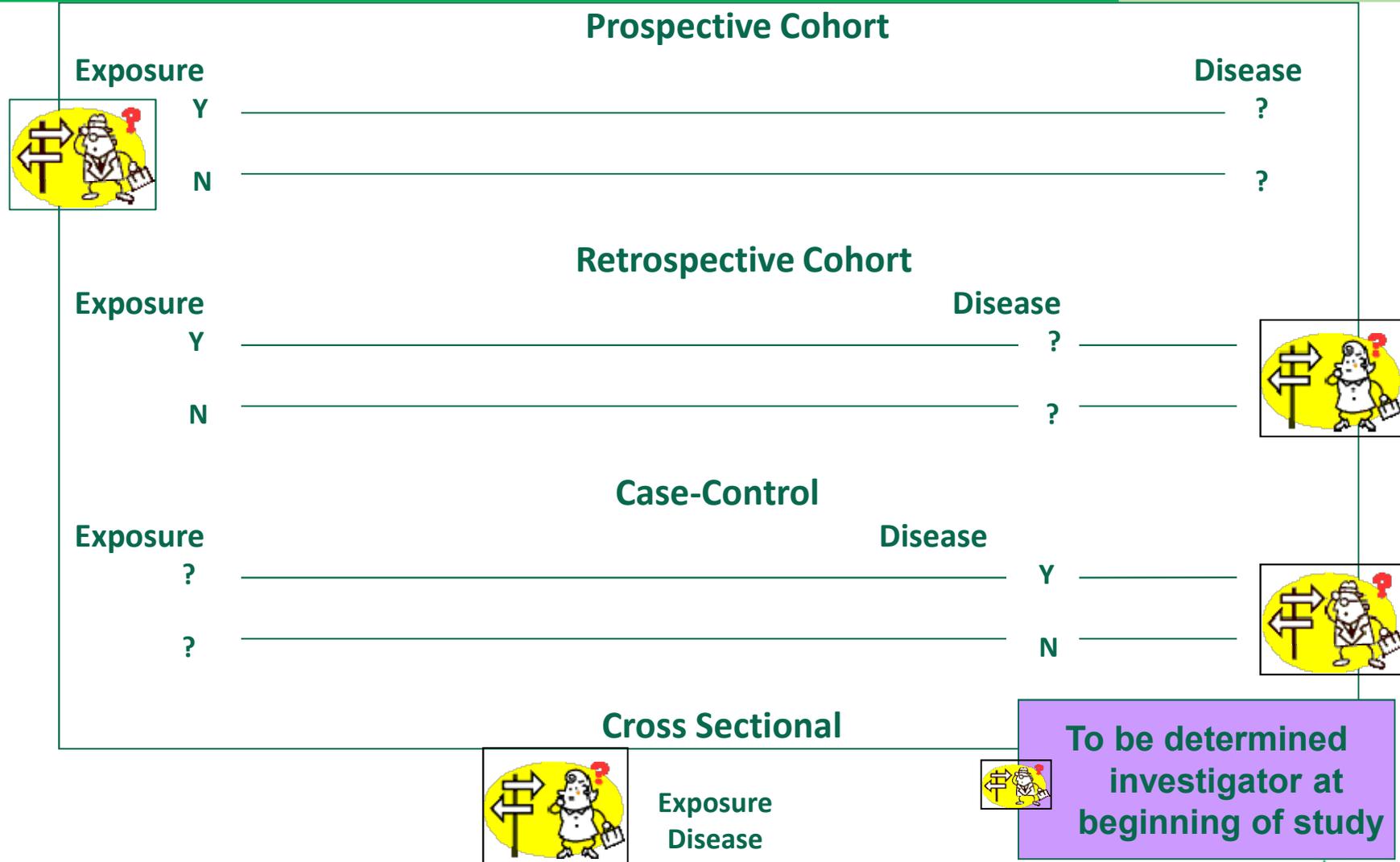
Study Design



Selection levels in different designs



Timing of exposure and outcome

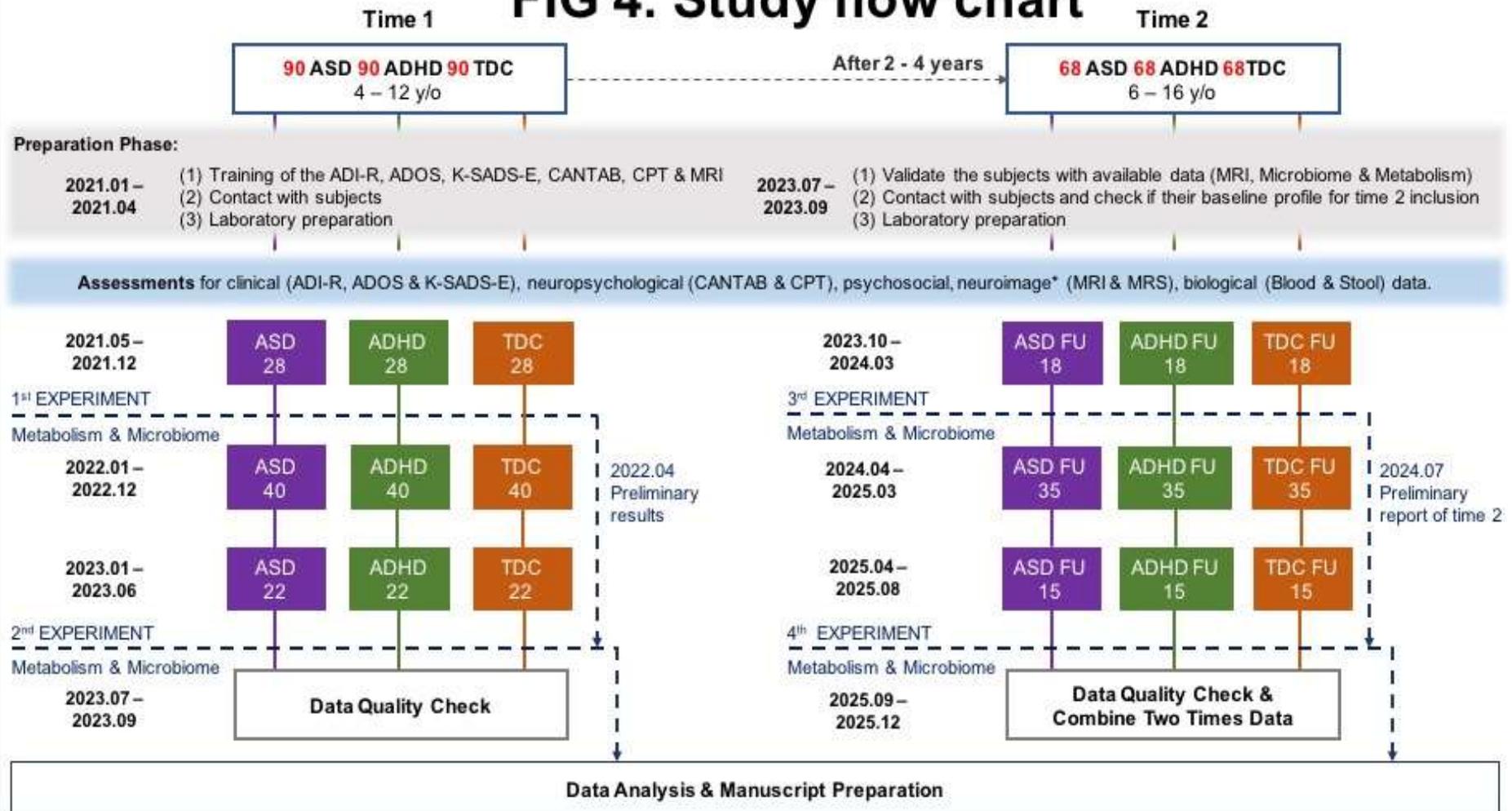


Research Design & Methods

- **Introductory Overview (optional)**
- **Study design, population, enrollment procedures**
- **Research instruments**
- **Follow-up procedures**
- **Definition and/or measurement of study exposures and outcomes**



FIG 4. Study flow chart

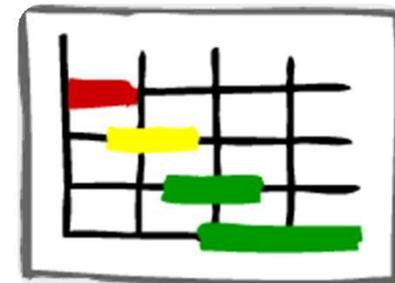


* The successful rate of neuroimaging for children subjects is around 80% according to previous studies.



Research Design & Methods

- Procedures for record review
- Data management
- Field operations
- Sample size
- Data analysis
- The logic strategy of the research plan
- Using tables and figures
- Timetable, Gantt Chart



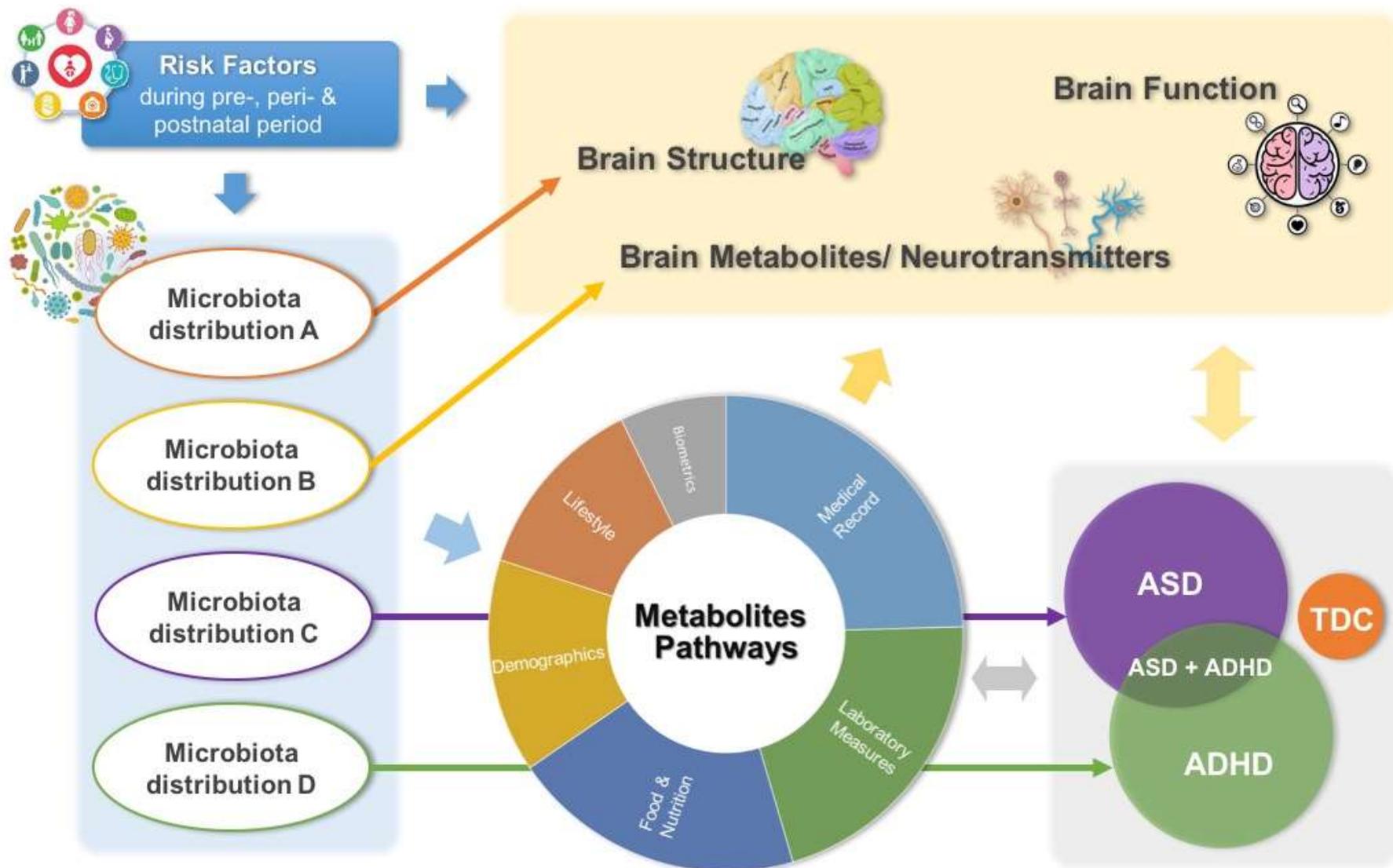


FIG 3. The study design diagram

Anticipated Results

- Satisfy the original hypothesis and the importance in the research plan
- Potential difficulties and limitations





Others

- **Human Subjects**
- **Potential Risks and Hazards**
- **Gene Recombination**
- **Animal Investigation**
- **References**

ADHD/ASD



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Outlines



**No grants,
No research,
No papers**

Review Criteria (MOST)

- **Novelty and Significance**
- **PI Performance**
- **Weakness and Suggestion**
- Environment and Facility
- Research Ethics
- Budget Structure/Overlapping with other projects
- **Peer Review** (Taiwan is small, you may know your reviewers), **2 primary reviewers and 2 secondary reviewers.**



Review Criteria (NHRI)

- **DESCRIPTION**
- **CRITIQUES**
 - **Significance (strengths & weakness)**
 - **Originality/Uniqueness (strengths & weakness)**
 - **Approaches (strengths & weakness)**
- **RESOURCES AND ENVIRONMENT**
- **INVESTIGATORS**
- **BUDGET**
- **OTHER CONSIDERATIONS**
 - **Research Ethics, Human subjects etc.**
 - **Mentoring (NHRI Career Development Grant)**
- **Reviewers** (not peer review but international reviewers mainly, who are ethnic Chinese)



What a grant reviewer concerns?

- **Personnel**
 - **Professional positions of key professional personnel**
 - Education, Previous employment, experience, and honors
 - **Previous research outcome**
 - Publications and record of serving as PI
 - **Feasibility**
 - Institutional Environment and Resources
- **Abstract**
- **Progress Report**
 - Previous related outcomes
 - Reviewers' comments
- **Budget**
 - For personnel, instruments, equipments
 - Other supports



Effort Preparing vs. Reviewing

COMPONENTS	Preparation Efforts	% Reviewer's Concern
Specific Aims/Hypotheses	1%	100%
Background/Significance	75%	~ 1%
Preliminary Results	9%	15%
Methods/Study Designs	15%	85%



Why Research Proposals Fail

- **Proposal deadlines not met**
- **Guidelines not Followed** (Read it carefully)
- **Proposal not Intriguing**
- **Proposal did not Meet Priorities**
- **Proposal Not Complete** (some sections missing)
- **Poorly written** (fonts, page limits, not organized or logical, sloppy [grammar, spelling, presentation, copy-and-paste, references])
- **Proposal Appears to be Beyond the Capacity of the Principal Investigator**
- **Proposal with weak Methodology** (Lacks direction: distinct aims, measurable objectives, analysis plans, future/impact)
- **Unrealistic or inappropriate Budget/Timeline**
- **Cost Greater than Benefits**



Why Proposals Fail-top 5 reasons

- **Lack of significance and originality**
- **Methodology flaw,**
- **Lack of clear hypothesis,**
- **Not following the research ethics**
- **Incomprehensible writing**





2020 NHRI
rejected

How to write a research proposal? By Susan Cox, M.D., Ph.D.

A Novel Multi-dimensional Prospective Study of the Gut-brain Axis through Metabolic MRI, Metabolomics and Gut Microbiome to Discover Gene-microenvironment Interactions in Neurodevelopmental Disorders

an over-optimistic assertion †

over-ambitious.

This study time-table may have to be revised to ensure project completion within the five-year research duration.

A large effect size of 0.8 was used in the sample size calculation. The large effect size might not be achievable and needs to be justified.

including maternal (e.g., maternal infection, obesity), prenatal/early-life (e.g., mode of delivery; gestational age) and environmental factors (e.g., second-hand smoke) may affect the gut microbiome.

II. CRITIQUE

The cited references and listed bibliographies were poorly annotated, making it very difficult to verify the technical validity to support some proposed approaches or evaluate the scientific context used to justify the substantive hypotheses.

1, even with a single wave only, could result in high-dimensional data each possibly with different inter-related components. Throughout the application, there was no mentioning of specific data analyses plans to handle these high-dimensional and likely correlated data (e.g., data reduction) or extract the informative constructs relevant to each specific aim and then conduct more well-defined statistical analyses (e.g., by latent profile analyses; neuropsychological network; pathway analyses).

Outlines



Resubmission of a proposal

- Do you know why your proposal was rejected?
- Did you reply all the comments?
- Did you revise the proposal according to the reviewers' comments?
- Do you think the proposed topic is still feasible and competitive? Change topic?
- Do you think the methodological flaw is fixable?
- There is no guarantee of a revised proposal being accepted.



2021 NHRI RESUBMISSION

Response to Previous Review Comments

We have revised the project with **dark red** highlights according to the reviewers' comments. Due to the strict page limit, we have tried our best to squeeze the added information to the original concise project.

II. CRITIQUE

#1 The cited references and listed bibliographies were poorly annotated, making it very difficult to verify the technical validityevaluate the scientific context used to justify the substantive hypotheses.

REPLY: Thank you very much for carefully review the project. We apologized for this careless mistake. I prepared the Form Section 5 in two files. The first file includes (A) Specific Aims, (B) Background and Significance, and (C) Previous and Current Studies. The second file includes (D) Research Design and Method, (E), (F), (I) and (J). I used EndNote to organize all the cited references. When I merged the files before submission, I thought the EndNote would automatically update the full citations based on my experience in many manuscripts and project preparation. I am sorry that I did not go through the number of citations carefully, so the references of the first file (234 citations) and second file (98 citations) did not merge because I did not click the "Update Citations and Bibliography." The final citations should be 313. We have carefully checked the references in this version and found the total citations are 346.

SIGNIFICANCE Strengths: Given the rich information from the comprehensive data collection, if the proposed specific aims are achieved;..... and/or risk stratification for future clinical research.

REPLY: Thank you for your positive comments.

Weaknesses: **#2** Although each of the proposed four Aims was logically laid out and accompanied by a stated hypothesis, very little specifics were given in terms of the relational structure and directionality of all the proposed multi-dimensional measures and what predictors to be expected for putatively positive vs. negative clinical outcomes.

REPLY: Thank you for raising this important question. Due to page limit and no literature documenting any causal inference of this novel project with multi-dimensional measures, the original project did not provide enough but some (B3.1.2, B3.3.2 & 3 in the original project) specific predictions for the outcomes. In this revised project, we have tried our best to strengthen the specifics in Aim 1 & 4 and the hypotheses, B.3.1, B.3.3.1 and B.3.3.7. The rationales and predictors involved are illustrated in B.3.3. Based on our hypothesis, we anticipate observing the impacts of intrinsic environmental factors (gut microbiota and metabolites) on the clinical, cognition, and brain structure and function outcomes. First, we anticipate that pre- and perinatal early environmental factors will affect the microbiome diversity in youth, that the dysbiosis of gut microbiota will influence the metabolites level in peripheral due to the poor nutrients up taking, or that the microbiota-dependent metabolism pathway has been interrupted. Moreover, we may observe from both peripheral metabolites level and the brain neurotransmitters via MRS, which combines

D



B

2021 NHRI RESUBMISSION

APPROACHES

Strengths: The multi-dimensional assessment... diffusion spectrum MRI (DSI)...The longitudinal study design... careful planning of the laboratory analyses of gut microbiome and metabolites.

REPLY: Thank you for your positive comments.

Weaknesses:

#4 Although TDCs will be matched to the identified cases with respect to age, sex, and geographic areas, the investigators should be advised to carefully evaluate whether and how the preclinical determinants (or common causes) of ASD and ADHD may affect their AIM1 to ensure the proposed study design is adequate and the planned comparative analyses are unbiased.

REPLY: Thank you for your valuable comments on the sample selection. Both ADHD and ASD will be incident cases recruited at both clinical and epidemiological settings. In order to minimize the selection bias and confounding from common early risk factors for ASD and ADHD as compared to TDCs, we will identify the early developmental exposures based on interviews and mother pregnancy medical records of all participants to eliminate the confounding effects from the common risk factors affecting ASD and ADHD, particularly given that co-occurrence of ASD and ADHD is around 25-27% (Mansour *et al.*, 2017, Simonoff *et al.*, 2008, van Steijn *et al.*, 2012, Zablotsky *et al.*, 2020). The prospective follow-up study design with two-wave repeated measures may also prevent the unknown exposures for both disorders. We will analyze the Time 1 data to identify the significant features that may leverage both ASD and ADHD, then evaluate these factors at Time 2 to verify whether the planned comparative analyses are unbiased. Please refer to the revised **Section 5 Aim 1 and Aim 2, D.1 research design, and D.6** statistical plan as well.

#5 For instance, recent studies have found that several neurodevelopmental risk factors, including maternal (e.g., maternal infection, obesity), prenatal/early-life (e.g., mode of delivery; gestational age) and environmental factors (e.g., second-hand smoke) may affect the gut microbiome.

REPLY: Yes, the environmental factors have been reported to be associated with ASD and ADHD. Our original project included maternal, prenatal, and developmental factors, but due to the page limit, we did not include a clear statement. Please refer to **Section 5 B.3.3.1** for maternal, prenatal/early-life, and environmental factors.



2021 NHRI
accepted

P011110A

A Novel Multi-dimensional Prospective Study of the Gut-brain Axis through Metabolic MRI, Metabolomics and Gut Microbiome to Discover Gene-microenvironment Interactions in Neurodevelopmental Disorders

This revised application retains the previously identified strengths: The proposal is novel and innovative, the research questions significant and important to clinical practice, methodological approaches state-of-the-art, the investigators preeminent, and the research environment outstanding.

including maternal (e.g., maternal infection, obesity), prenatal/early-life (e.g., mode of delivery; gestational age) and environmental factors (e.g., second-hand smoke) may affect the gut microbiome.

prospective design that follow up the subjects from birth or even *in utero*. Removal of AIM1 and part of AIM4 that use retrospective information would strengthen further the proposed study.

The Review Committee approved this proposal with an overall rating of Outstanding and this project will be supported for a duration of 5 years.

ADHD/ASD

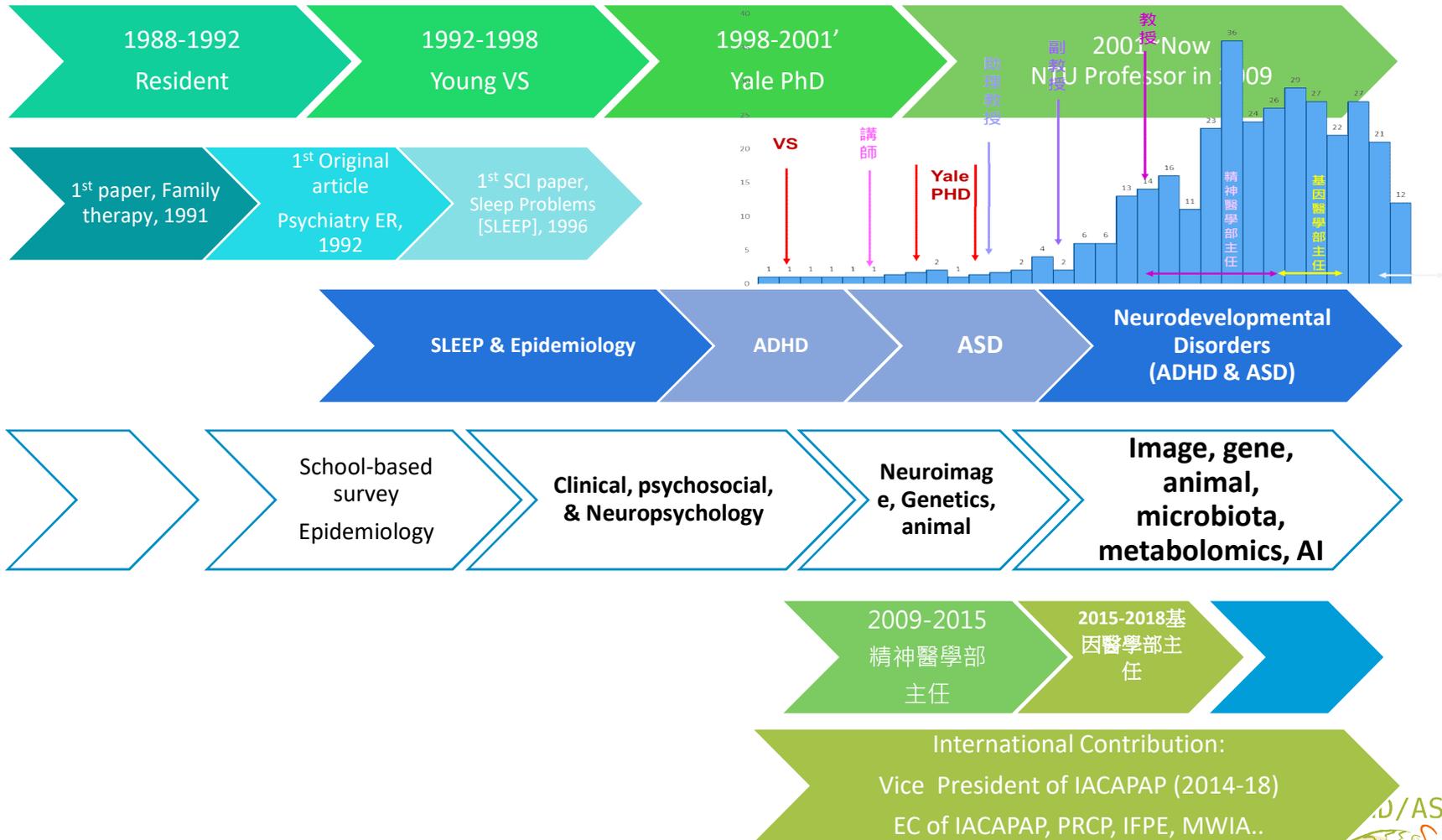


SUSAN GAU'S LAB

Outlines



Career Development



Current Research Projects

2013	2014	2015	2016	2017	2018	2019	2020	2021
ADHD, Sib, MRI (NSC) ASD, Sib, MRI, ERP (NSC)							ASD microbiome, metabolomics, images FU (5-year)	
ADHD Adult FU (NHRI)		ASD FU Study (NHRI)					ASD/ADHD, microbiome, metabolomics, images, FU (5-year)	
		ASD CNV research (MOST)			ASD NGS + metabolomics+ iPSC			
		Adult ADHD image, ERP endophenotype (MOST)			Adult ADHD image F-U			
School-based internet study-a 4-wave F-U study (MOE)		Epidemiology of Child mental disorders (MOHW)			ASD 照護計畫			
MOST, NHRI, NTUH, MOHW, MOE								

長期追蹤

社區流行病學
臨床精神醫學

神經心理功能
認知內表現型

結構及功能性
腦造影

腦造影
內表現型

藥物認知
影像學

認知影像
基因學

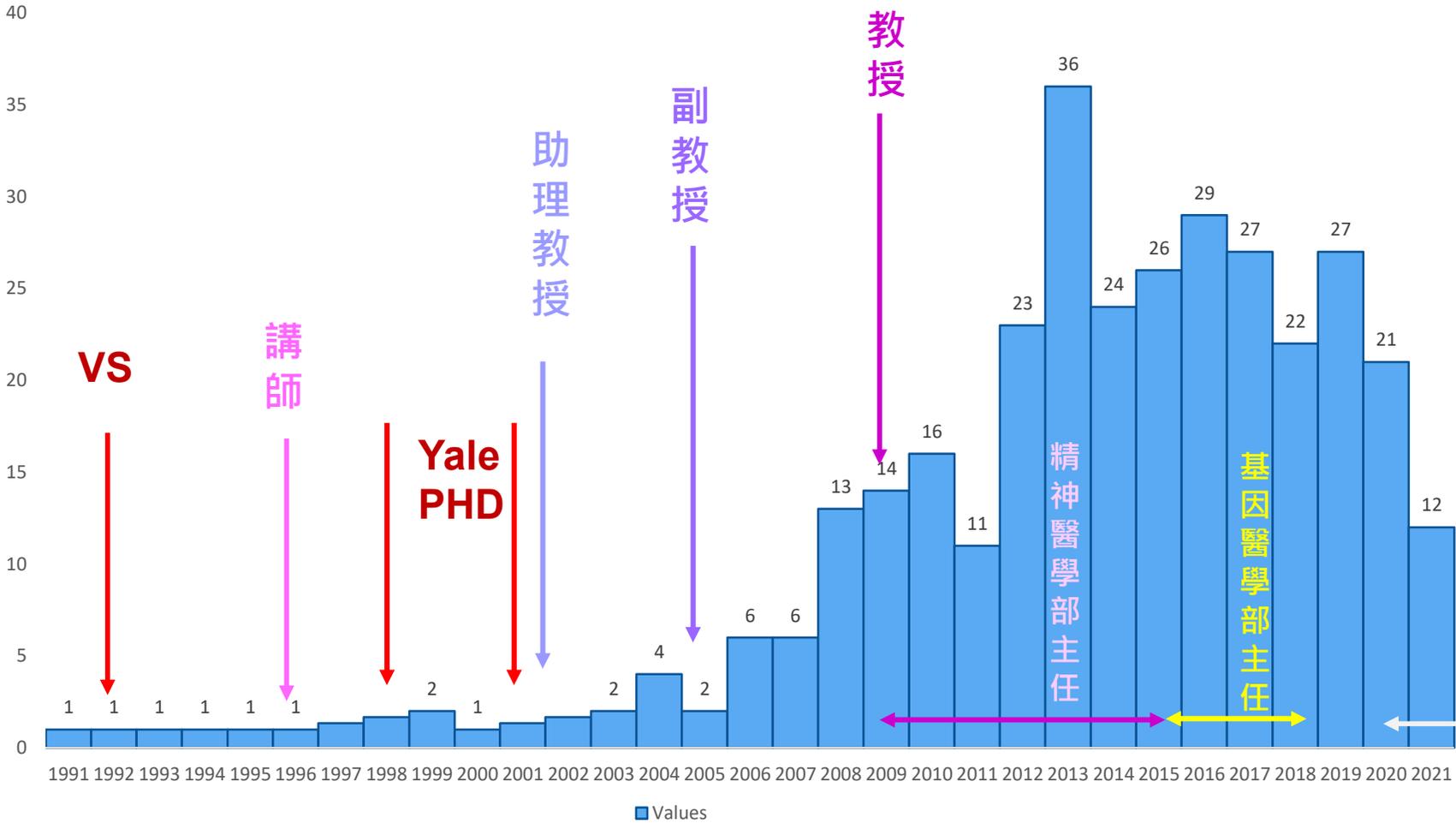
代謝體、腸內
菌及微生物學

建立中文化評估工具信效度

ADHD團隊之研究發展

果蠅ADHD模式

SCI/SSCI papers from 1991 till 2021 0410





How to write a research proposal? By Susan Gau, M.D., Ph.D.

Thank you for listening Q & A



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