Designing the Scientific Approach

Jeffrey (Jerry) Jarvik, MD MPH
Departments of Radiology, Neurological Surgery, Health Services
Comparative Effectiveness, Cost and Outcomes Research Center

ASNR/RSNA CERT ~~5/30/18~~ 6/20/18

Acknowledgements

- NIH: UH2 AT007766; UH3 AT007766
- NIH P30AR072572
- Larry Kessler, for his generous sharing of slides

Disclosures

- Physiosonix (ultrasound company): Founder/stockholder
- UpToDate: Section Editor
- Evidence-Based Neuroimaging Diagnosis and Treatment (Springer): Co-Editor

U.S. Department of Health and Human Services

Supported by the

National Institute of Arthritis and Musculoskeletal and Skin Diseases

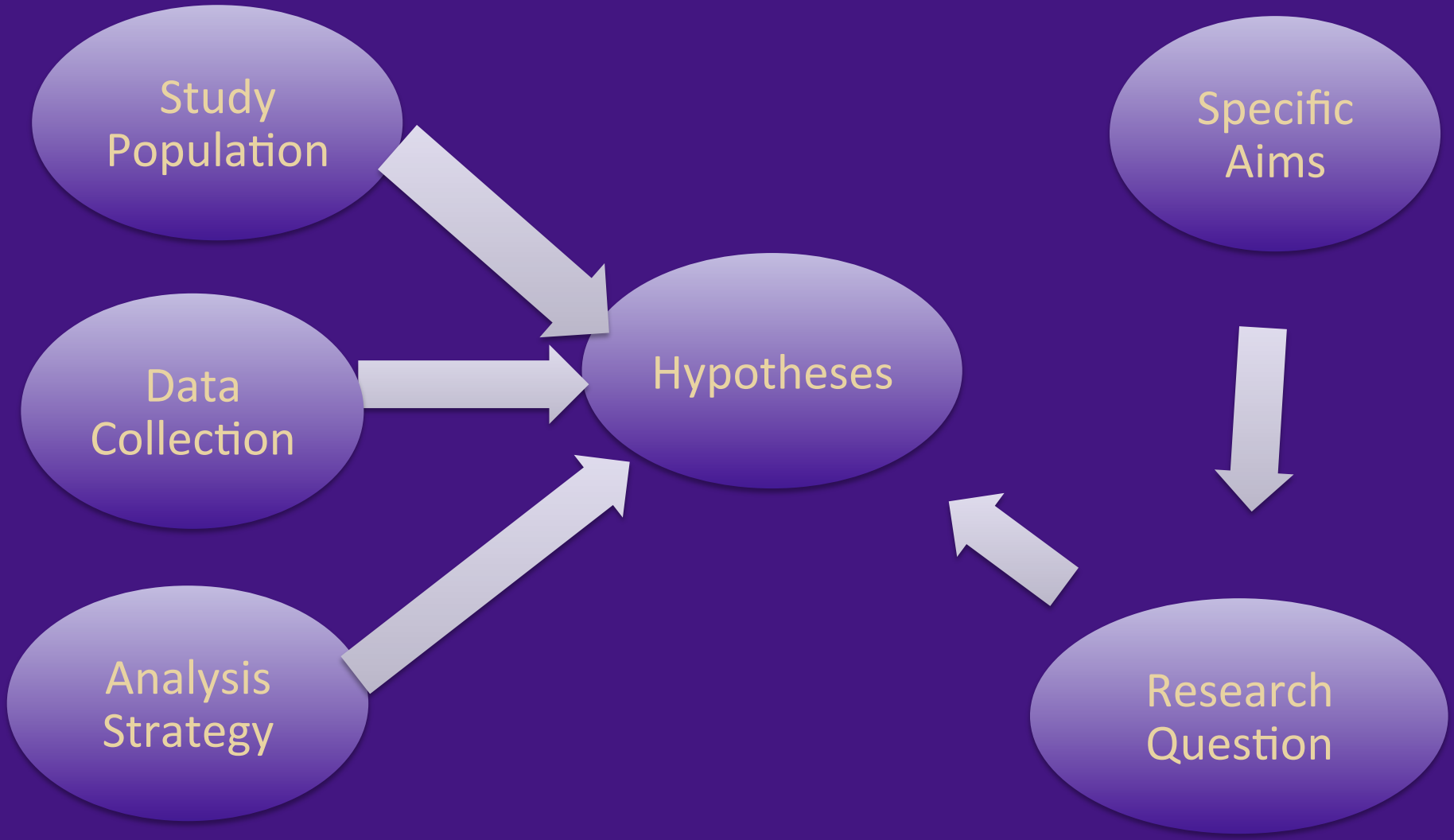
References

- Science: How Not to Kill a Grant Application
  http://www.sciencemag.org/careers/2000/08/how-not-kill-grant-application-part-6-developing-your-research-plan
- PHS 398 https://grants.nih.gov/grants/funding/phs398/phs398.html
- Science: How to Write an NIH Grant
  http://www.sciencemag.org/careers/2000/06/how-write-nih-grant-application

Outline

- Basics of the approach/methods section
- Approach "The NIH way"
  - Active trials/observational research vs secondary data analyses
- Section by section
- Summary

Approach Section "Mission"



Methods and This Course

- Connect *Methods* to *Specific Aims* and *Innovation:* Failure will doom grant
- Very different study types
  - Active trials with participants(often pts), includes observational studies
  - Secondary data analyses
- NOT discussing biomarker discovery

Outline

- Basics of the approach/methods section
- Approach "The NIH way"
  - Active trials/observational research vs secondary data analyses
- Section by section
- Summary

Contents of NIH 424 Application: form 398

1. Introduction to Application
2. Specific Aims
3. Research Strategy (Significance, Innovation and **Approach**)
4. Inclusion Enrollment Report
5. Bibliography and References Cited/Progress Report Publication List
6. Facilities and Resources
7. Protection of Human Subjects
8. Targeted/Planned Enrollment
9. Inclusion of Women - Minorities
8. Inclusion of Children
9. Vertebrate Animals
10. Select Agent Research
11. Multiple PD/PI Leadership Plan
12. Consortium/Contractual Agreements
13. Letters of Support (e.g. Consultants)
14. Resource Sharing Plan(s)

PHS 398 Application Research Plan

Section	Pages
Introduction (resubmission only)	1
Specific Aims	1
Research Strategy: (Significance including a **very** short background, Innovation)	~2
Approach: Relevant preliminary studies	~1
Overall strategy and methodology including data collection	~5
Analysis, power, interpretation	~3
Resource sharing, potential problems/strategies, benchmarks, feasibility, risk management	~1

12 Pages

Page Limits

- **Follow the page limits unless the FOA specifies otherwise.**
  - –All tables, graphs, figures, diagrams, and charts must be included within the Research Strategy page limit.
  - –If PAs or RFAs contain specific page limits, those instructions always supersede these instructions.

Career Development Awards

- Have special forms and procedures
- K01, K08, K22, K23, K99 – all slightly different paths and not all available from all Institutes/Centers
- Challenge: how much focus on the study (R01-like) vs. on training
- Ask successful K-mentors

Approach – NIH Definition

- Describe the *overall strategy, methodology, and analyses* to be used to accomplish the specific aims of the project. Unless addressed separately in the *Resource Sharing Plan*, include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.

Approach- Definition (cont.)

- Discuss *potential problems, alternative strategies and benchmarks* for success
- If in the early stages, describe strategies to *establish feasibility and address management of high risk aspects*

Outline

- Basics of the approach/methods section
- Grant planning
- Approach "The NIH way"
  - Active trials/observational research vs secondary data analyses
- Section by section
- Summary

Approach (10 pages)

1. Preliminary studies*
2. Research Methods/Study Design*
3. Study Population*
4. Measures
5. Data Collection/Procedures
6. Data Management
7. Statistical Analyses
8. Statistical Power
9. Potential Problems, Timeline and Milestones

1. Preliminary Studies Include:

1. Relevant Studies by PI and Study Team
2. Pilot Data
3. Laboratory, Procedures, Feasibility
4. Survey Instrument Reliability and Validity
5. Data Management, Safety and Monitoring

Preliminary Studies: What Goes Where?

Preliminary Info	Comment
Relevant studies and team experience	Usually *Prelim Section*; in *Significance* if it drives hypotheses
Pilot Data	*Prelim*; in *Significance* if these drive hypotheses
Lab feasibility	*Prelim* section
Instruments	*Prelim*; unless you have developed a measure, then in measurement
Data Management	*Prelim* section

Preliminary Studies for New Applications

- PD/PI's prelim studies, data, and/or experience pertinent to application
- Prelim data usually essential part of application
- Reviewers instructed to place less emphasis on the prelim data from Early Stage Investigators

Note: if prelim studies drive hypothesis then they are part of significance

End Prelim Studies with Summary Paragraph

Conclusions from Pilot Study: Our pilot work demonstrated that it was feasible to perform our study at two different institutions. Most importantly, both patients and clinicians readily accepted randomization to one of two diagnostic studies. Clinicians also cooperated with answering pre-imaging and post-imaging questionnaires, an important aspect of evaluating diagnostic impact. The outcome measures performed as we had hoped, changing in the predicted directions over time. The measures suggested some outcome differences that favored the rapid MRI. Finally, our pilot study provided us with data on the variance of key variables for sample size calculations.

2. Overview of Research Methods

Give complete synopsis in one paragraph (PICOTS+)

- What kind of study (design)
- Participants
- Interventions (recruitment, treatment)
- Comparator
- Outcomes (Data collected/key variables)
- Timing
- Setting
- Analysis (specific aims)
- Power (sample size)

2. Methods Overview

- "To compare a rapid MRI vs. plain x-rays of the lumbar spine as the initial imaging modality in patients with low back pain, we will perform a randomized controlled trial involving three independent medical facilities in Seattle. We will identify patients when their primary care clinician orders plain x-rays for the lumbar spine, and will follow them for 1 year after enrollment. Our primary outcome measures will be functional status and health related quality of life instruments. Our target enrollment number is 372 patients."

2. Research Methods

- Conceptual model or framework drives grant
- Well thought out design
- Scientifically sound study population
- Feasible recruitment strategy
- Measurements clearly defined, instruments justified for exposure, outcome, other variables
- Follow-up plan that maximizes efficiency
- Data management described

Conceptual Frameworks, Model, Rationale

- A conceptual framework is the mechanistic, biological relationship among variables or a formal theoretical model that underlies your research
- Every study has a conceptual framework, whether you like it or not
  - Articulates relationships among concepts/variables
  - Is clear and logical
  - Is consistent with Specific Aims
  - Is ad-hoc, mechanistic or based on a formal theory
  - Is operationalized with specified concepts, measures of these concepts, and an analytic approach

Where to Add the Conceptual Framework?

- In *Significance* if an existing model is key to your Aims
- In *Innovation* if a new or revised model will be part of or the focus of your *Approach*
- In *Approach* if an existing model is used to
  - Determine study design
  - Select/organize variables
  - Develop an intervention or structure analysis

Active vs. Existing Data Studies

- Active Studies
  - RCTs
  - Prospective studies
  - Specimens from existing studies and creating "new" data, e.g., new interpretation on existing images correlated with outcomes
  - Design is crucial
- Existing Data Studies
  - Data collected for other studies
  - Data base studies or secondary data studies, e.g., administrative claims data
- Many threats to validity, both internal and external

2. Research Methods – Study Types

- Qualitative or Mixed Methods: in vogue – make sure appropriate
- Descriptive
- Case-Control
- Cohort; Nested Case-Control/Case-Cohort
- Randomized Trial (pay attention to blinding)

Consider implications in terms of source of participants, cost, feasibility…

2. Research Methods: Active Trials

- RCTs – the "gold" standard
  - Options, e.g., individual or cluster RCT; parallel vs. stepped wedge
- Active quasi experiments
  - Threats to internal validity
  - Threats to external validity
- Prospective cohort studies
- Retrospective-prospective studies

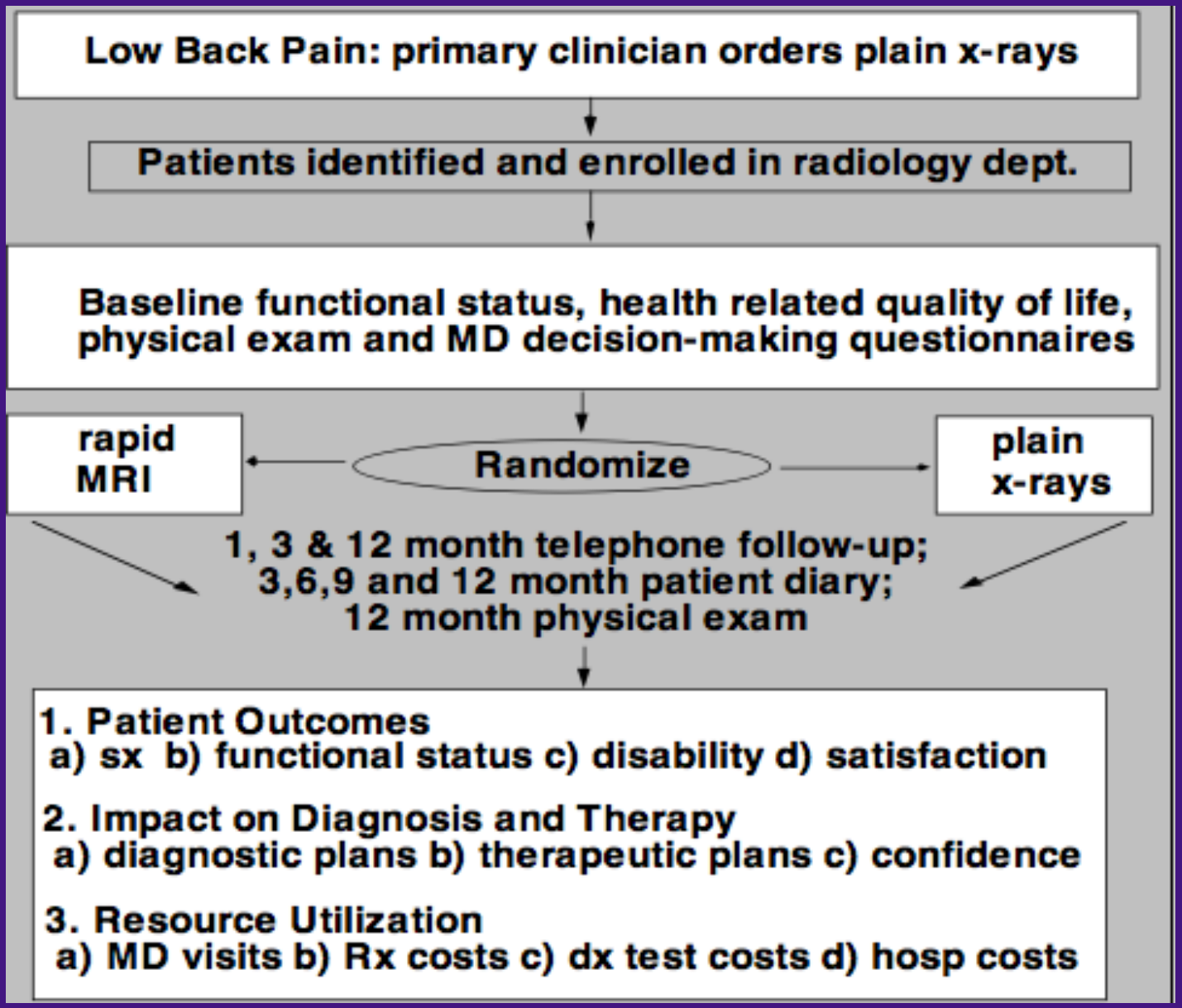
Trial Issues

- Note the audience for the study – NIH different than FDA, PCORI, etc
- Multi-site trials – why they are critical in certain situations
  - –Strengthens generalizability
  - –Critical where site/operator may affect intervention, e.g., IR
  - –Feasibility re #'s of subjects

Secondary Data Issues

- Do not fit hypothesis to data- develop hypothesis as if you had "all the data in the world"
- Then determine if the compromises are too great to continue

Study Design Example



3. Study Population

Study population should be justified in terms of the Specific Aims

- Age, Sex, Race/Ethnicity, Geography
- Healthy enough to participate and live long enough to contribute information
- Oversample based on exposure?
- Special inclusion/exclusion criteria

Inclusion/Exclusion Based on ICD-9

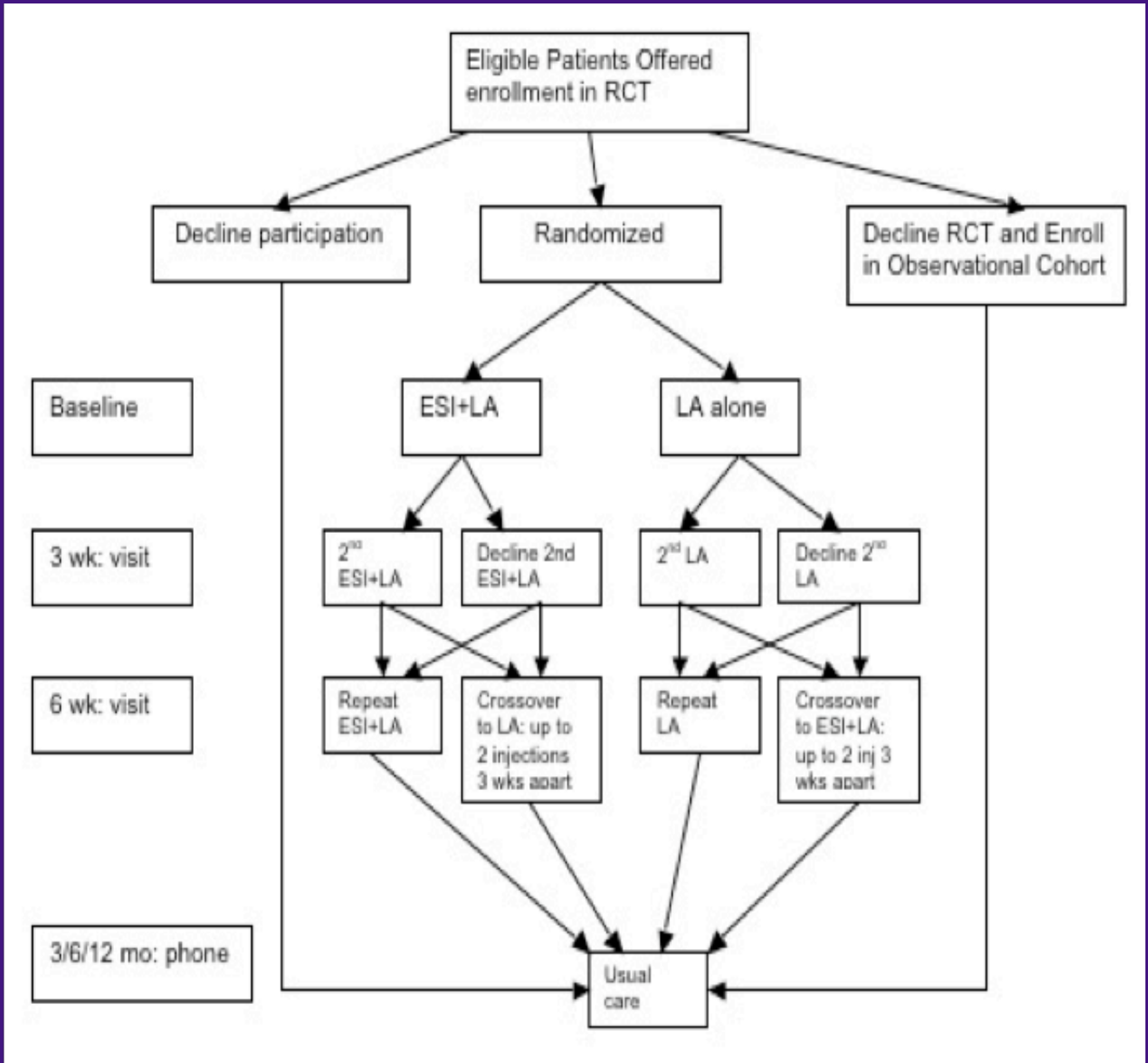
Table 5.5. ICD9 Inclusion and Exclusion Codes for Observational Cohort	
Inclusion Diagnoses	**Exclusion Diagnoses**
(721.3) Lumbosacral spondylosis w/o myelopathy	(140-239.9) All neoplasms
(721.5) Kissing spine (BaastrupDx)	(324.1) Intraspinal abscess
(722.1) Lumbar disc displacement w/o myelopathy	(630-676) Pregnancy-related diagnoses
(722.2) Degeneration of intervertebral disc site unspecified	(720.0-720.9) Inflammatory spondyloarthropathies
(722.3) Schmorl's nodes	724.3 Sciatica
(722.5) Degeneration of thoracic or lumbar intervertebral disc	(730-730.99) Osteomyelitis
(722.52) Degenerative disc dx, lumbar	(733.1, 733.10, 733.13, 733.95) Pathologic fx, incl unspecified site (733.10) or vertebrae (733.13), stress fracture of other bone (733.95)
(722.6) Degeneration of intervertebral disc, site unspecified	(733.8, 733.81-733.82) Non-union/mal-union of fracture
(724) Other & unspecified disorders of back	(05-806.9) Fractures of spinal column
(724.0) Spinal sten. other than cerv	(839-839.59) All vertebral dislocations
(724.2) Lumbago	(E800-E849.9) Vehicular accidents
(724.4) Back pain w/ radiation, unspec.	
(724.5) Backache, unspecified	
(847.2) Lumbar strain	

Inclusion/Exclusion for RCT

Table 5.4 Inclusion and Exclusion Criteria for RCT	
Inclusion Criteria:	Exclusion Criteria*
1. Pain in the low back, buttock, and/or lower extremity (pain NRS≥5) with wt bearing activities (buttock/leg>back pain).	1. Cognitive impairment that renders the patient unable to give informed consent or provide accurate data.
2. Modified Roland-Morris score of at least 7.	2. Clinical co-morbidities that could interfere with the collection of data concerning pain and function.
3. Mild to moderate lumbar central canal spinal stenosis (Boden et. al. criteria(77)) identified by MRI or CT scan within 12 months of enrolment.	3. Severe vascular, pulmonary or coronary artery disease which limits ambulation including recent myocardial infarction (within 6 months).
4. Lower extremity symptoms consistent with neurogenic claudication.	4. Spondylolisthesis requiring surgical fusion (i.e., greater than 5mm of slippage).
5. Must be able to read English and complete the assessment instruments.	5. Previous lumbar spine fusion surgery.
6. Age 65 or older.	6. Severe osteoporosis as defined by multiple compression fractures or a fracture at the same level as the stenosis.
	7. Metastatic cancer.
	8. Excessive alcohol consumption or evidence of non-prescribed or illegal drug use.
	9. Possible pregnancy or other reason that precludes the use of fluoroscopy.
	10. Concordant pain with internal rotation of the hip (or known hip joint pathology).
	11. Active local or systemic infection.
	12. Abnormal coagulation.
	13. Allergy to local anesthetic, steroid or contrast.

Participant Flow Chart

Figure 5.2 ESI RCT Flow Chart



Outline

- Basics of the approach/methods section
- Grant planning
- Approach "The NIH way"
  - Active trials/observational research vs secondary data analyses
- Section by section
- Summary

To Summarize

- *Be able to* connect the specific aims, research question, and hypotheses through the approach by identifying the study population, collecting appropriate data, and using the best tools to analyze the data.

Outline

- Basics of the approach/methods section
- Grant planning
- Approach "The NIH way"
  - Active trials/observational research vs secondary data analyses
- Section by section
- Summary
- Bonus Tips

Tips

- Read the instructions, multiple times
- Make sure the design is clear, including the underlying logic
- Be clear how you will use the info collected
- Reviewers will question each statement- anticipate and pre-answer

Tips (cont.)

- Identify potential weaknesses (show to others)
- Plan Bs (in case primary method fails)
- Be focused, but remember “big picture” context
- Don’t overwhelm reviewer with facts and jargon
- Proofread!

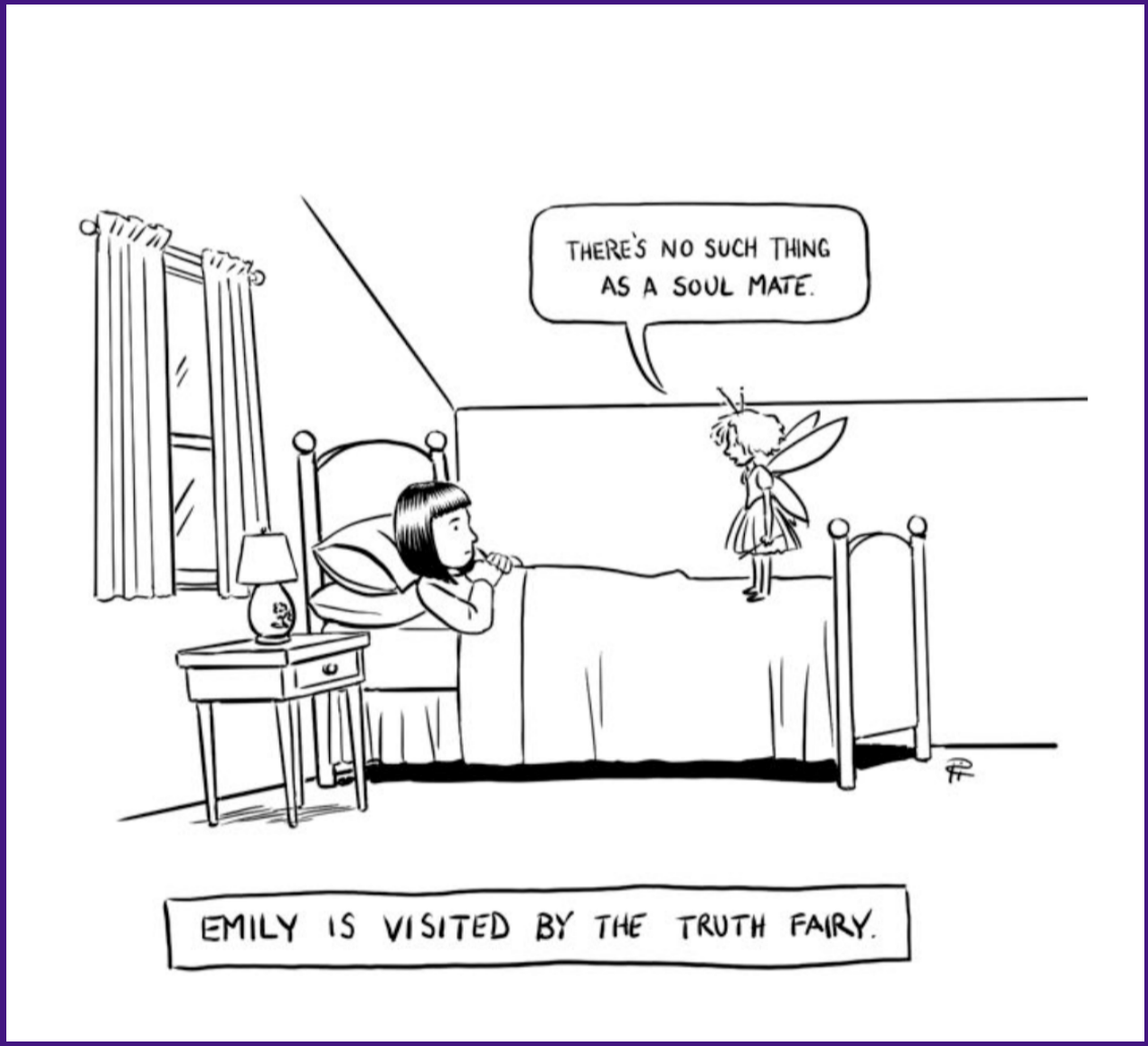
Tips from NIH https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/write-your-application.htm#Your%20Research%20Plan

1. Make goals realistic: “overly ambitious”=kiss of death
2. Be organized and logical: Headings, subheadings, diagrams, bullets
3. Clear and concise language
4. Sell your idea

Tips from NIH https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/write-your-application.htm#Your%20Research%20Plan

5. Edit, with friends
6. Share for comments

Questions?


THERE'S NO SUCH THING AS A SOUL MATE.
EMILY IS VISITED BY THE TRUTH FAIRY.