Hypothesis-testing, Hypothesis-generation, Pilot Studies, in Clinical Research Areas

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The Scientific Method--Ideally

Exploration/Hypothesis Generation:
- Past Published Research (Clinical & Basic);
- Clinical Experience and Observation,
- Secondary Data Analyses with Personal/Shared Data
- Exploratory Studies

HT Execution

Hypothesis Formulation

HT Design

Pilot Study

HT Conclusions

Publications

Data Sharing

Independent Replication & Validation

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Hypothesis Formulations

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HT Conclusions Publications

As is:
Hypothesis-Testing (HT): The heart of clinical research

Required: Each “a priori” hypothesis must have scientific rationale and empirical justification.

Required for EACH SPECIFIC hypothesis:

- Research Protocol (Sampling, Measurement, Design)
- Analytic Plan
- Testing criteria
  - Significance level
  - Adequate Power
Crucial Questions

Where do you get STRONG hypotheses to be tested without well-done exploratory studies?

Where do you get the information needed to test those hypotheses most effectively and efficiently (design and power) without well-done exploratory studies?

How can you be sure that what you propose to do in a hypothesis-testing study is feasible without well-done pilot studies?
How can you do hypothesis-generating or pilot studies without funding?

Since reviewers confuse the types of studies, the criteria for evaluating one type of study are often applied to another type, which confuses researchers.

Researchers misrepresent hypothesis-generating as HT, or badly designed HT as “pilot” studies, which confuses reviewers.

**Researchers=Reviewers!!!**

- Clarification of these issues is necessary for productive communication between researchers and reviewers and with the research and clinical communities.
What is an Hypothesis-Generating (Exploratory) Study?

A **large** study on a relevant population meant to explore certain phenomena in order to generate important and innovative hypotheses for future testing.

... and to generate information relevant to designing those studies most cost-effectively.

Phase I, Phase II trials?
Hypothesis to be developed: Some gene (multiple candidates) is related to diagnosis D (Onset? Type? Severity? Course? Treatment Resistance?), perhaps in conjunction with certain environmental influences (multiple candidates).

Possible moderating or mediating relationship between genes and environment on D may exist: Does the result differ according to ethnicity or gender?

Hypothesis to be tested: Gene G moderates the effect of E on the onset of disorder D on patients between the ages of 15 and 30.
What is a Pilot Study?

A pilot study is a **small** study done as a preliminary study to a hypothesis-testing study, in which research tactics intended for a hypothesis-testing study are tried out.

- A feasibility study
- An effort to “debug” the proposed design.
Major Contrasts

A hypothesis-generating study focuses on **research questions** to be answered in the future, and is **large**.

A pilot study focuses on **tactics** used to answer research questions, and is **small**.
How Large is Large?

In HT, a sample size large enough to yield 80% power to detect (5% significance level) any effect size above the threshold of clinical significance.

- May be as few as 10 subjects per group, to as many as thousands per group.

In Hypothesis-generating, sample sizes similar to those generally used in HT to follow, if not larger, large enough to get credible effect sizes.

In Pilot studies, only enough to convince the user and reviewers that the tactic will work.
Evaluating a proposal for an exploratory study

Yes:
- Are the issues not yet well researched or well understood but of clinical importance?
- Is the study, if it proposes to collect new data, ethical?
- Is the sample representative of a clinically relevant population and large enough?
- Are the measures comprehensive enough to shed light on the issues and of good enough quality (reliability, validity, sensitivity) to shed light on the issues?
- Have examples of important questions been articulated to show the direction of researchers’ thinking and to support their lack of bias and analytic and interpretative skills?

No:
Evaluating a Proposal for a Pilot Study

YES:

- Are the issues in the HT-to-be under consideration of clinical importance?
- Are the feasibility questions to be addressed in the pilot study pertinent and important to the design of the HT?
- Under what conditions would what is seen in the pilot study discourage proposing doing the main study or changing its design (tweaking)?
- Is it clear that if the HT were found to be feasible, the researchers would submit a proposal for that HT as a R01?

NO:

The Bottom Line with Pilot Studies

You don’t want to find out after the HT study is started that you’ve made mistakes in the protocol that invalidate the testing, or make it unlikely that credible results can be obtained!
Conclusion

A badly designed, underpowered hypothesis-testing study is neither a pilot study, nor an exploratory study.

Well-designed exploratory studies are necessary to having strong hypotheses in hypothesis-testing studies and the information necessary to design them well.

Well-conceived pilot studies are necessary to avoid catastrophes in hypothesis-testing studies.

What to do to clarify clear communication between researchers and reviewers, and to foster the proposals, funding, and publication of good science?