CHAPTER 10

APPROACH SUBSECTION OF RESEARCH STRATEGY: RESEARCH DESIGN, EXPECTED OUTCOMES AND POTENTIAL PROBLEMS & ALTERNATIVE STRATEGIES

Approach is a subsection of the *Research Strategy* section. Its format is given below:

APPROACH:
- Each Aim:
  - Introductory Paragraph
  - ~~Justification & Feasibility~~
    - ~~Review of Relevant Literature~~
    - ~~Preliminary Studies~~
  - Research Design
  - Expected Outcomes
  - Potential Problems & Alternative Strategies
- Timeline
- Future Directions

One of the changes to this Chapter pertains to the format for the Approach subsection, which is reproduced, above. "Justification and Feasibility" and its two subdivisions have been lined out because, with the new approach that we recommend, they are no longer part of the Approach subsection. (We have moved them to the Significance subsection, Chapter 9). Without those components, the formatting for each aim "collapses" to include the Introductory Paragraph, Research Design, Expected Outcomes and Potential Problems & Alternative Strategies.

More substantive changes in this Chapter pertain to the Research Design subsection. Three of NIH's new foci, rigorous experimental design for robust and unbiased results, authentication of key biological/chemical resources, and consideration of relevant biological variables should be addressed as part of the Research Design sub-subsection. What follows is a general overview of those changes. Extra requirements may be imposed by individual Institutes and Centers, either on their website or in Funding Opportunity Announcements that they issue. Additional specific requirements of that kind would take precedence over the general instructions.

Additional aids to understanding how you can enhance reproducibility are in video format. You can access all of them at http://vcastsearch.nih.gov/NIH/main.jsp. Type "Reproducibility of Data Collection and Analysis" into the search box and they will come up, ready for viewing. They are:

- Reproducibility of Data Collection and Analysis – Modern Technologies in Cell Biology: Potentials and Pitfalls (11-24-2014)
- Reproducibility of Data Collection and Analysis – Modern Technologies in Structural Biology: Potentials and Pitfalls (03-13-2015)
- Reproducibility of Data Collection and Analysis – Modern Technologies in Genome Technology: Potentials and Pitfalls (06-04-2015)

- NIH Workshop on Reproducibility in Cell Culture Studies (09-28-2015 Day 1 and 09-29-2015 Day 2)
- Improving Openness and Reproducibility of Scientific Research (10-26-2015)

Rigorous Experimental Design for Robust and Unbiased Results

One of the problems that NIH has identified is that some – many? – investigators have not received sufficient training in "strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results." As a consequence, results of their research may not be replicable when the 'same' experiments are repeated using appropriate design. If you are one of those persons, it is relatively simple to catch up. Many texts and journal articles that describe what constitutes rigorous experimental design for qualitative, quantitative and mixed-methods research can be found by searching the Internet using available search engines. They range from ones that are general/philosophical (e.g., http://www.sfn.org/Advocacy/Policy-Positions/Research-Practices-for-Scientific-Rigor) to others (e.g., http://www.stat.cmu.edu/~hseltman/309/Book/Book.pdf) that are chapter-by-chapter guides. Still others (e.g., http://www.stat.cmu.edu/~hseltman/309/Book/Book.pdf) provide links to resources at other sites. Many of the publications would appear to be discipline specific. However, the principles and fundamentals of good experimental design and analysis are generally applicable across disciplinary boundaries. As an alternative approach to finding the sought-after resources, consult your reference librarian.

Unfortunately, rigorous design alone won't get you all the way to where you need to be. How you implement the design is also important, particularly if you are doing bench research. If you aren't doing so already, adhering to principles of Good Laboratory Practice is something that we recommend you consider. Although the original principles were intended to improve studies of drug safety, in our opinion they extend to any laboratory in which investigators want to produce results that are replicable. As defined by the Medicines and Healthcare Products Regulatory Agency (UK), Good Laboratory Practice procedures provide "a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. … GLP helps assure 'regulatory authorities' [read as 'NIH'] that the data submitted are a true reflection of the results obtained …" You can find manuals describing Good Laboratory Practice by searching the Internet. For example, the World Health Organization offers a *Handbook – Good Laboratory Practice (GLP)* at http://www.who.int/tdr/publications/documents/glp-handbook.pdf. While putting into practice all that is described would probably not be practicable, coming as close as possible should be your goal, in our opinion: Stating in a grant application that you adhere to applicable principles of Good Laboratory Practice would be a strong indication that you are serious about the issue of reproducibility. Many of the practices are simple to implement and can make a big difference with respect to others being able to replicate your work. For example, having a standardized format and worksheets for record keeping is essential, as is a full set of standard operating procedures for your research group. The latter is even more important if a multi-laboratory effort is proposed, as would be the case for a Research Program Project (P01) application. Little things, like having the checking the accuracy of your scale on a routine basis, or keeping hygroscopic chemicals in either a desiccator or under a vacuum, or putting dates on reagent containers so that shelf life can be monitored may seem tedious at first, but will prove to be well worth the trouble in the end.

Routine **Authentication of Key Biological/Chemical Resources** is a very important part of Good Laboratory Practice. NIH's definition of a "key" resource is one that is critical to the conduct of the proposed research and has a characteristic or characteristics that could cause variation laboratory to laboratory. NIH provides the examples of "cell lines, specialty chemicals,