CRU Protocol Application Guidelines

The General Clinical Research Center (CRU) of the Translational Science Institute is part of a national network of research centers sponsored by the National Center for Research Resources (NCRR). The CRU provides a setting for National Institutes of Health (NIH) supported patient oriented, peer-reviewed investigator research. The CRU also provides space for industry sponsored patient clinical research. The CRU collaborates with many areas of the Medical Center to provide varied services to investigators. Our CRU can provide nursing support, core laboratory and genetics laboratory processing, metabolic kitchen and nutrition support, imaging services, informatics, and biostatistician expertise for the investigator. A safe subject protection environment, combined with a highly trained research staff, ensures that studies are conducted in a supportive environment.

The eIRB system is used to apply for CRU resources. It is important to contact the CRU personnel when you apply to the CRU. As you work on the application, you may want to contact the CRU for information and help. The CRU staff will be pleased to meet with each investigator and study coordinator to answer any questions regarding the application process. The phone numbers of staff members are listed below.

http://eirb.wfubmc.edu

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Application Guidelines for Clinical Research Unit (CRU) "Pilot" Studies

Literature Definitions of Pilot Studies:

Simon Day, 2nd Edition: A small study for helping to design a larger study. The main uses of pilot studies are: (a) to test practical arrangements (for example, how long do various activities take? is it possible to do all the things we want to do?), (b) to test questionnaires (e.g., do the subjects understand the questions in the way we intended?) and (c) to investigate variability in data.

"Pilot study" is a small preparatory investigation that is in no way intended to directly investigate or test the research hypotheses of interest. As such, most pilot studies are not publishable - although there certainly are exceptions. (P.W. Stewart; UNC CRU)

A Dictionary of Epidemiology (John M. Last, 3rd Edition): A small-scale test of the methods and procedures to be used on a larger scale if the pilot study demonstrates their feasibility (i.e., that these methods and procedures can work).

Pilot Study Goals:

One of the missions of the CRU is to support the development of novel early stage scientific projects. These are projects that have a strong likelihood of future extramural funding, but are at a stage where funding has not yet been obtained and not competitive for extramural funding without additional preliminary data or information. This guideline does not refer to any specific request for proposals or funding mechanism. The purpose of this document is provide guidance to potential investigators (with or without additional funding) on the types of pilot studies which can be supported by the CRU, and the services that the CRU/RCU can provide (see Services section for more details).

The goal of this CRU program is to support pilot studies focused on the acquisition of key information (examples provided below) that will markedly enhance the likelihood of success for extramural funding applications within the near future (1-3 years). Typically, the CRU will not provide ancillary support of ongoing funded studies. Additionally,

these pilot grants will typically not support addition of another unfunded endpoint to a previously approved study unless the investigators can clearly outline the potential for the additional endpoint to provide new future extramural funding (distinct from the funding of the ongoing study).

Evaluation Criteria:

The following questions will be used to evaluate the significance and potential for extramural funding of pilot project applications:

1. Is the underlying question of sufficient importance?
2. What is the investigator's plan for the larger study?
3. How the information from the pilot will be used to refine subsequent studies?
4. Does the measurement being evaluated operationalize the concept being studied?
5. How feasibility is defined and will be established?
6. Is there clear demonstration of financial need?
7. Is the track record of the investigator or investigation team sufficient to suggest they are able to complete the study and make the transition from pilot to full study? (less important for junior faculty or new investigators)

Additional questions may be also considered in the review. CRU staff will be available to provide guidance and further information prior to submission to optimize the likelihood of a successful application.

Pilot Study Types (for more specific examples, see Appendix 1):

Pilot Type	Description	Example	Key features
Measurement Refinement	A systematic investigation of the characteristics of a measurement to optimize its use in future research	Studies of intra-individual and inter-observer variability, and other variance components.	The case for investigating the factor to be measured is good. Protocol isolates and focuses on variance components of interest.
Outcome variance for sample size estimation	Establishing the frequency or distributional characteristics of the intended study outcome.	To establish estimates of variances, correlations, and/or differences for use in power calculations that will guide selection of a sample size for the full-scale study.	The hypothesis using this outcome should be important. Outcome should be valid. Sample sizes will vary but are typically small. Results will be used to better estimate sample sizes for future studies.
Feasibility Pilot	An investigation of the ability of key study components to achieve the operational aims.	To evaluate the total cost or timeliness of doing the experiment. In this case a sample size even as low as N=1 may be sufficient. Example: Recruiting and randomizing older person with mild cognitive impairment to an exercise regimen	The case for performing the larger study must be strong. Protocol of the pilot anticipates the planned protocol of the larger study as closely as possible.

Of note: Pilot study sample sizes are typically small but may vary widely based on the specific needs (scientific and budgetary) of the study and will be an important component of the review process. The committee advises all applicants to contact CRU support staff to discuss sample size estimates prior to submitting application to minimize delays and increase the likelihood of success.

Available CRU Services:

The following GAC services are available on request within pilot study applications:

- Outpatient clinic visits
- Nursing support

- Study coordinator support
- Nutrition support (meals and nutritionist consultation)
- Informatics (database development and storage)
- Safety Review
- Statistical support (design and sample size/power estimates)
- "Ancillaries"
    - clinical laboratory analyses
    - imaging studies
    - meals

Budget Guidelines:

The budget for each pilot application will be reviewed based on its own scientific merit and potential for future extramural funding. The majority of the services outlined above (except "ancillary services") are typically available with minimal limitations, but cannot be guaranteed as the demand and number of competing studies varies widely. There is not strict budget cap for ancillary studies. However, the budget should be appropriate for a pilot study. Typically, budgets of successful applications will be modest (typically no more than $30,000) and of short duration (typically between 6 - 18 months).

Applicants will be required to submit information regarding all existing and pending funding support, both external (e.g. federal, foundation, industry) and internal (e.g. Intramural Research Support). Funding support information will be included in the review process (i.e. a clear demonstration of financial need).

Appendix 1

10 Specific Examples or pilot studies with references:

1) Develop hypotheses/Explore associations

Vanderbilt et al. Asthma severity and PTSD symptoms among inner city children: a pilot study. J Trauma Dissociation 2008; 9:191-207.
Recruited a small sample of children with asthma in a registry to assess association with PTSD.

Currie et al. Age and functional correlations of markers of coagulation and inflammation in the elderly: functional implications of elevated crosslinked fibrin degradation products (D-dimers). J Am Geriatr Soc 1994;42:738-42.
Pilot within a larger study - preliminary look at coagulation and inflammatory marker distribution in 18 young and 18 old individuals – used those results in larger sample of 282 older adults with varying levels of function – correlate D-dimer levels, mostly higher for physically impaired - **an example of how a pilot might be done within an RO1 or other larger/funded study**

2) Small/non-definitive study to gather date regarding an initial hypothesis

Samani et al. Telomere shortening in atherosclerosis. Lancet 2001;472-473.
Cellular dysfunction associated with senescent cells might contribute to development of atherosclerosis, telomere length a measure of cell senescence - compared a measure of telomere size in leukocyte DNA from 10 persons with severe CAD and 20 controls without CAD – telomere lengths were shorter in CAD than controls

Berry et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma.
N Engl J Med 2006;354:697-708.
TNF alpha activity increased in severe asthma, measured in 10 severe asthma, 10 mild asthma, 10 non-asthma controls, found significant upregulation/activity TNF-alpha

3) Develop instruments, measures or methodologies

Mohile et al. A pilot study of the Vulnerable Elders Survey-13 compared with comprehensive geriatric assessment for identifying disability in older patients with prostate cancer who received androgen ablation. Cancer 2007;109:802-10.
Title self-explanatory – 50 patients, found VES-13 identified disability nearly as well as CGA

Cavanaugh et al. Using step activity monitoring to characterize ambulatory activity in community-dwelling older adults. J Am Geriatric Soc 2007;55:120-124

Explore the potential of using step activity monitoring to detect differences in ambulatory activity with increasing age and decreasing function – 30 young, 28 independent elders, 12 functionally limited elders.

4) Test feasibility of intervention or recruitment

Susini et al. Radiofrequency ablation for minimally invasive treatment of breast carcinoma. A pilot study in elderly inoperable patients. Gynecologic Oncology 2007;104:304-310.

Katula et al. Lifestyle interventions and independence for elderly pilot study: recruitment and baseline characteristics. J Am Geriatric Soc 2007; 55:674-683.

5) Estimate sample size for full scale trial

*Rejeski et al. The lifestyle interventions and independence for elders (LIFE) pilot study: design and methods. Contemporary Clin Trials. 2005:141-154.

An extraordinary pilot study due to its multicenter, 400 subject size and randomization to physical activity vs. successful aging education followed for one year – for multiple goals (see pub), all to collect the info needed to do a large scale investigation.

6) Establish forms, procedures, data systems, working relationships

Taylor et al. Pilot study of the incidence and prognosis of degenerative Parkinson disorders in Aberdeen, United Kingdom: Methods and Preliminary Results. Movement Disorders 2006;21:976-982.

Test methods to be used in a larger study of PKD – forms, data systems, case finding techniques – from subpopulation of people in Aberdeen found 202 possible PKD, 50 confirmed as probable PKD – plan to use methods in large population based study

7) Evaluate efficacy in small number patients at a single site

Berry et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma.
N Engl J Med 2006;354:697-708.

TNF alpha inhibitor – etanercept improved QOL, FEV1 in severe asthma compared to placebo

8) Phase I and II drug trials

Ginsberg et al. The ALIAS Pilot Trial: a dose escalation and safety study of albumin therapy for acute ischemic stroke: physiological responses and safety results. Stroke 2006:37:2100-6.

Done in 82 subjects with stroke to determine if feasible, safe

Creticos et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. N Engl J Med 2006;355:1445-55.

RCT of novel conjugate vaccine immunostimulatory sequence of DNA with a specific ragweed allergen (binds to TLR receptor in DC cells which inhibits T help cells) in 25 individuals over 6 week period of vaccine – follow-up allergic rhinitis

9) Initial evaluation of diagnostic test characteristics

Shah et al. Utility of lumbar puncture in the afebrile vs.febrile elderly patient with altered mental status: a pilot study. J Emergency Med 2007;32:15-18.

Retrospective chart review 125 elderly patients with altered mental status and lumbar puncture with CSF --- 41 had fever of which 10 (24%) had abnormal LP – 84 did not have fever, of which 15 (18%) had abnormal LP

10) Initial test of new technology

*Collacott et al. Bipolar permanent magnets for the treatment of chronic low back pain. A pilot study. JAMA 2000;283:1322-1325

RCT crossover in 20 patients magnet vs. sham, held in place over area of pain by Velcro binder – one week magnet or sham, one week washout, one week opposite magnet or sham - found no difference