Writing a Successful Grant Application

Applying for a grant to facilitate the completion of clinical or translational research can be a daunting task. Resources are not infinite, and the reality is that most grant applications are not successful. However, the likelihood of a successful application can be increased by following a strict algorithm that ensures the applicant's passion, skill and scientific approach are clear to those evaluating the application.

The format for grant applications varies depending on the funding source of the grant. There are several key components that are germane to a grant application that are worthy of discussion. Each component is as important as the next and, when read together, allows the reviewer to appreciate the research project in its entirety. To facilitate a better understanding of how to articulate the various components of a grant application, examples have been taken from a successful application titled "Does metal hypersensitivity develop following temporomandibular joint total joint replacement, and does it correlate with patient reported outcomes?"

The six key components of a grant application generally include the following:

Hypothesis

This should be a single sentence that conveys the essence of the research project. There should be several specific and measurable aims that follow the hypothesis.

Example

"The investigators hypothesize that temporomandibular joint total joint replacement (TMJR) with a cobalt chromium molybdenum titanium condyle and a titanium/ultra-high molecular weight polyethylene fossa device will result in the development of measurable metal hypersensitivity at 12 months after implantation."

- *Specific Aim 1: Does metal hypersensitivity develop in previously device-naïve patients who undergo a TMJR?*
- *Specific Aim 2: What is the clinical significance of metal hypersensitivity following TMJR?*
- *Specific Aim 3: Does metal hypersensitivity correlate with patient reported outcome measures?*

Background and Significance

It is important to establish early the population that stands to benefit from the research project.

It also is important to discuss the most up-to-date literature in terms of supporting scientific evidence as well as deficiencies within the scientific literature that make the proposed research project valuable. The background should focus on the following:

- A brief discussion of the epidemiology and prevalence of the disease, condition or intervention being investigated that directly speaks to the potential impact on a population from the research project.

- A critical discussion of relevant literature provides context for the research project, illustrates the investigator's knowledge and understanding of the subject and describes how the research project will address a fundamental gap in the scientific literature.
- Pilot data, when available, are key to providing preliminary data that will both support the research project and facilitate a sample size and power calculation.
- Why is the research question important and how many stand to benefit from its revelations?

Example
"The number of TMJR performed within the US and internationally continues to grow. Current data projections suggest that by 2023, almost 7,000 TMJR will be completed in the US alone with an additional 5,500 procedures internationally… Although a revision rate of 1% for TMJR represents a small number of the potential 12,500 TMJR that are implanted per year (125 TMJR/year), there remains a very real possibility that metal hypersensitivity may develop in a much larger group of patients and result in increased pain, decreased function and reduced Quality of Life (QoL). There are currently no prospective clinical studies on the development of metal hypersensitivity in orthopedics or oral and maxillofacial surgery that have used Leukocyte Transformation Testing (LTT) to identify metal hypersensitivity and correlate with Patient Reported Outcome Measures (PROMs).

Preliminary Studies
The volume and quality of previous studies may vary. On rare occasions, no data exist – which typically means the researcher is required to perform a simpler research project to obtain pilot data prior to any grant application.

- The data that are chosen should be as robust as possible as it will be the foundation for the proposed research project and will often be used to appropriately power the study and determine the sample size that is needed
- All references should be appropriately cited within the grant application.

Example
"Metal hypersensitivity has been reported following implantation of many orthopedic devices. It is more common with total hip arthroplasty (THA) as a result of the metal on metal (MoM) design. It appears to be much less common with metal-on-polyethylene (MoP), ceramic-on-ceramic (CoC) or ceramic-on-polyethylene (CoP) devices. It is thought to result in 1-3% of failures for the typical metal-on-polyethylene (MoP) total knee arthroplasty (TKA). The development of metal hypersensitivity or the progression of pre-existing metal hypersensitivity following TKA is thought to potentially result in one of four presentations that can be considered clinically significant including persistent pain following device implantation; the development of localized swelling, erythema, pruritus and eczema; the development of systemic contact dermatitis (SCD) and device failure."

Design and Methods
Research methodology varies in quality, resulting in many studies that are unable to withstand critical review – rendering the results and conclusions meaningless. Research methodology

must, by its very nature, be robust to help ensure the outcomes measured are real and that bias and confounding are eliminated or reduced to a minimum. The following key elements should be present:

- Well-defined inclusion and exclusion criteria *(e.g., which reduce heterogeneity and confounding and define the population of interest for the study*
- Primary predictor variable(s) *(e.g., TMJTJR)*
- Primary outcome variable *(e.g., LTT)*
- Secondary outcome variables *(e.g., metal ion levels, patient reported outcome measures, pain, maximum incisal opening, dermatitis)*
- Data collection components and the specific time points at which they are obtained (*e.g., baseline T0 and 6(T1), 12(T2) and 52(T3) weeks after TMJTJR)*

Statistics

Involvement of a statistician prior to the grant application is paramount. This will help identify potential confounding and bias that will facilitate the research methodology for the project as well as allow appropriate sample size and power calculations. Determining whether continuous, nominal or ordinal outcome measures are chosen is important. Continuous variables tend to provide the best opportunity to detect differences between groups with smaller sample sizes and a higher sensitivity. It is generally important to have some understanding of the anticipated means and standard deviation or errors of the primary outcome measure particularly for the control group. The following are key areas that require consideration:

- Identify the difference (delta) that is being measured in the primary endpoint and at what time points. Is the difference clinically relevant and measurable?
- Determine the desired effect size. The larger the effect size, the more significant and practical the difference is likely to be.
- Determine the Alpha and Beta errors. The Alpha error is typically set at 0.05 meaning that the likelihood of identifying a difference between groups that *Does Not Really Exist* is 5%. The Beta error is usually set at 80% or 90% meaning that the likelihood of identifying a difference between groups that *Really Does Exist* is 80% or 90%.
- Provide a sample size calculation. This can often be completed easily using online tools such as https://clincalc.com/stats/samplesize.aspx.
- Describe the statistical analyses that will be applied and to what data. This is often complicated when repeat measures analysis, multiple regression analysis and post-hoc analysis are needed.
- Describe a statistical plan for any missing data

Example

To determine the sample size and power calculation for the TMJR study the researchers provided the following table. The researchers determined that a difference of 1 on a continuous scale from 0 to infinity on the LTT was clinically relevant when comparing the LLT test at T0 (pre-operative) and T3 (12 months post TMJR) within subjects (assuming a rather large and conservative standard deviation of 2). This allowed a moderate effect size of 0.5

N	*Power*	*Alpha*	*Delta*	*SD*	*Effect Size*
34	*80*	*0.05*	*1*	*2*	*0.5*
10	*80*	*0.05*	*2*	*2*	*1.0*
6	*80*	*0.05*	*3*	*2*	*1.5*
44	*90*	*0.05*	*1*	*2*	*0.5*
13	*90*	*0.05*	*2*	*2*	*1.0*
7	*90*	*0.05*	*3*	*2*	*1.5*

Budget

The budget is relatively straight forward, but it has to be practical. The budget should include the following:

- A clear timeline
- Study coordinator support
- Statistical support
- Salary support
- Data housing *(e.g., Redcap)*
- Other study costs *(e.g., equipment, calibration)*
- Anticipated travel

Reviewing the Grant

The process for grant review depends on the organization proving the funding (NIH, NIDCR, foundation or industry). Generally speaking, the review process will address several areas. To be successful, it is helpful when the grant application is finalized and ready for submission to have an independent and qualified researcher review the project to ensure that all areas of importance are clear to someone not involved in the study. An independent review prior to submission will identify areas that need clarification and improvement prior to the submission. The planned research project and grant submission should strive to articulate the following:

- Impact of the project and who will benefit.
- Project significance and why this research project should receive priority over another research project.
- Investigator experience and commitment to the project. The former can be challenging for a new investigator without a track record, but this can be overcome with a well-thought-out and robust research project that addresses an important question.
- Innovation of the project. Repeating a previous research project without addressing a fundamentally new question will not be successful. The more innovative the research project, the better.
- The approach to the project must be rigorous and scientific. The methodology must eliminate as much bias and confounding as possible. This provides the reviewers with optimism that the study will have internal validity and therefore the likelihood of external validity.

- The environment in which the research project will take place must be able to support the project in terms of infrastructure, protected time and research facilities/staff.
- The budget must be realistic.