Grant Writing – Tips and Tricks

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Outline

I. Rationale for protocol

II. Elements of a protocol

III. Tips for success

I. The importance of a protocol

- Scientific integrity
- Obtaining funding
- Publishable
- Increasingly required

II. Elements of a protocol

1. Introduction/Background/Rationale
2. Research Question/Objective/Aims/Hypotheses
3. Study Design and Methodology
4. Analysis
5. Sample size (w/wo Power Calculation)
6. Ethics
7. Knowledge Translation and Exchange Strategy
8. Research team/environment
9. Timeline/Feasibility
10. Strengths and Limitations
11. Significance/Impact

1. Introduction/Background/Rationale

- Introduction and background will "build the case" for your study and frame the problem
  - The introduction needs to draw the reader in and place the study in context
  - Need to provide the evidence as to why this study is needed
    - Literature, reviews, previous research
  - **Clear** and **Compelling**
- Conceptual model/frameworks orient the design, data collection and analysis
  - Makes explicit how the research questions/objectives tie to methodology

Models for building the study rationale

- Deficiencies model (Creswell, 2014)
  1. State the research problem
  2. Review the studies that have addressed the problem
  3. Indicate deficiencies in the studies
  4. Advance the significance of the study for particular audience
  5. State the purpose statement

Example

Clostridium difficile Asso (CDAD) is the most frequent cause of nosocomial diarrhea in ind tries. Recent reports show an increase in the incidence, severity and relapse of CDAD in Canada and the U.S. Severe CDAD and relapse are the two most important complications of CDAD, and are associated with significant morbidity and mortality. The first-line therapy of CDAD consists of oral metronidazole. Oral vancomy djuvant tr been suggested (immunoglobulins, intra mycin, IV etc.) for the more complicated cases. It is difficult to determine, earl , which patient will develop complicated CDAD and therefore which patient would benefit the most from close follow-up and adjuvant therapies. Validated clinical prediction rules for complicated CDAD may help clinicians choose which treatment or management strategy to offer reover, they could be used to define a group of high-risk patients to sign of trial of new and costly therapy. A multi-centre prospective cohort study of hospitalized adults in Ontario and Quebec is proposed to derive and validate prediction rules of the risk for developing severe CDAD and/or relapse.

High burden

Problem is getting worse

Health effects are serious

Care gap

Proposed solution

What the study will do and how it will fill the gap

Conceptualization of the issue

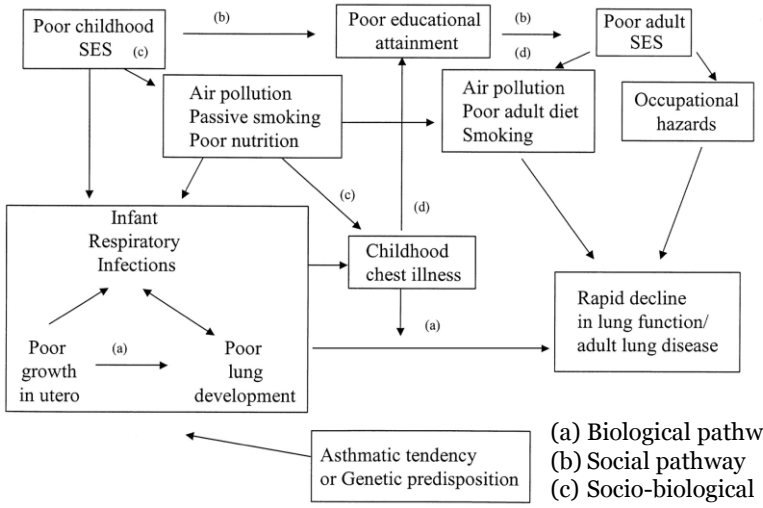
"Let the data speak for themselves, those scientists demand. The problem with this argument is, of course, that data never do speak for themselves"
Keller (1985)

- As a researcher, you will be constructing, analyzing, and representing the data under certain theories or assumptions
- The only way one can assess if your approach is appropriate is if you make these aspects clear (*a priori*)

The importance of articulating the conceptualization of your problem

- You and the reader becomes clear on your understanding of the problem
- The assumptions of the problem are explicit
- The logic of the design and the analysis are grounded (in theory or gleaned from evidence)
- Useful for organizing, integrating and framing
  - Helps plan the data collection/use and analysis

Schematic representation of biological and psychosocial exposures acting across the life course that may influence lung function and/or respiratory disease.



(a) Biological pathway
(b) Social pathway
(c) Socio-biological pathway
(d) Bio-social pathway

Ben-Shlomo Y , and Kuh D Int. J. Epidemiol. 2002;31:285-293

2. Research Question/Aims/Hypothesis

- Research aim/objectives/hypothesis should clearly frame your study and identify its parameters
- Spend time on making it as tight as possible, as it will greatly facilitate the other elements of your protocol

The importance of a good research question

- "*The question must not be tailored to fit the data – instead the question must be important in its own right*" (Naylor et al, CMAJ 1996)
- "*One third of a trial's time between the germ of your idea and its publication in the NEJM should be spend fighting about your research question*" (Prof. David Sackett - quoted in Riva et al. 2012)

What is the purpose of your study?

- Descriptive?
- Methodological?
- Evaluation?
- Treatment efficacy?

- **AIM: General goal of research**
  - Broad, visionary
- **OBJECTIVE(S): Specific statements of intent**
  - Specific – clear indications of your research, design and intent
  - Analyses should be obvious fit with these objectives
- **RESEARCH QUESTION(S)**
  - Overlap, sometimes alternative, to objectives or aim
  - Framed as a question, which the research aims to answer
- **HYPOTHESIS: *A priori* outcome of research that will be tested; Expectations from the researcher**
  - Can be based on previous literature, theory, pilot work ect…
  - Important to frame your analyses

3. Study Design and Methodology

- Heart of your proposal

➢ To best of your ability, you are to:

- **Identify** threats to validity and address in design (or analysis)
- Explicitly discuss how you plan to **address the threat** in the design or analysis.

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Common threats to validity to address

- Confounding
- Selection bias
- Bias in measurement
- Temporal measurement issues
- Bias due to missing data
- Incomplete exposure/outcome ascertainment
- Misclassification

ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions

Jonathan AC Sterne,[1] Miguel A Hernán,[2] Barnaby C Reeves,[3] Jelena Savović,[1,4] Nancy D Berkman,[5] Meera Viswanathan,[6] David Henry,[7] Douglas G Altman,[8] Mohammed T Ansari,[9] Isabelle Boutron,[10] James R Carpenter,[11] An-Wen Chan,[12] Rachel Churchill,[13] Jonathan J Deeks,[14] Asbjørn Hróbjartsson,[15] Jamie Kirkham,[16] Peter Jüni,[17] Yoon K Loke,[18] Theresa D Pigott,[19] Craig R Ramsay,[20] Deborah Regidor,[21] Hannah R Rothstein,[22] Lakhbir Sandhu,[23] Pasqualina L Santaguida,[24] Holger J Schünemann,[25] Beverly Shea,[26] Ian Shrier,[27] Peter Tugwell,[28] Lucy Turner,[29] Jeffrey C Valentine,[30] Hugh Waddington,[31]

Table 1 | Bias domains included in ROBINS-I

Domain	Explanation
Pre-intervention	**Risk of bias assessment is mainly distinct from assessments of randomised trials**
Bias due to confounding	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline
Bias in selection of participants into the study	When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical This form of selection bias is distinct from confounding—A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention
At intervention	**Risk of bias assessment is mainly distinct from assessments of randomised trials**
Bias in classification of interventions	Bias introduced by either differential or non-differential misclassification of intervention status Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias
Post-intervention	**Risk of bias assessment has substantial overlap with assessments of randomised trials**
Bias due to deviations from intended interventions	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s) Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).
Bias due to missing data	Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders
Bias in measurement of outcomes	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects
Bias in selection of the reported result	Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis)

the bmj | *BMJ* 2016;355:i4919 | doi: 10.1136/bmj.i4919

Study design considerations

- Population
- Variables (Measurement)
- Design features

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PLOS | MEDICINE

GUIDELINES AND GUIDANCE

The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement

Eric I. Benchimol[1,2]*, Liam Smeeth[3], Astrid Guttmann[2,4], Katie Harron[3], David Moher[5], Irene Petersen[6], Henrik T. Sørensen[7], Erik von Elm[8‡], Sinéad M. Langan[3‡]*, RECORD Working Committee[¶]

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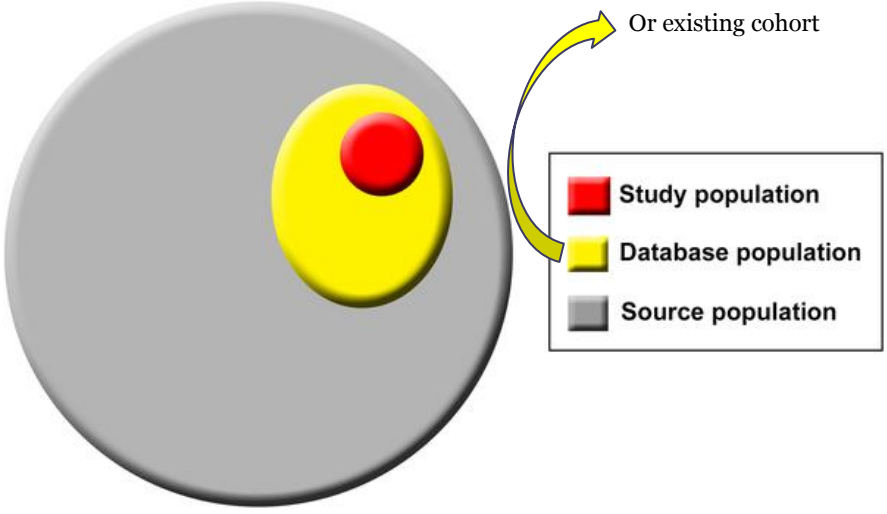
Fig 1. Population hierarchy in studies using routinely collected data sources.



Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, et al. (2015) The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS Medicine 12(10): e1001885. doi:10.1371/journal.pmed.1001885
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001885

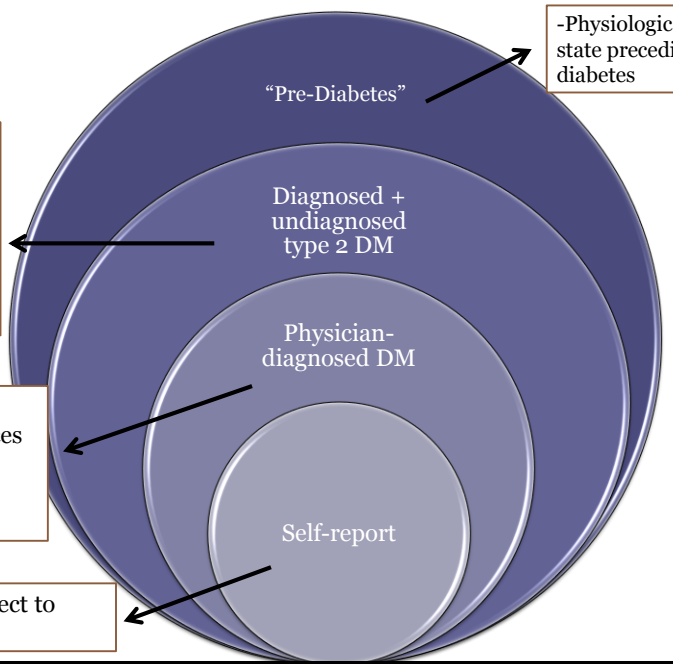
Variables in the study

- Why do you need them?
- What is their role ?
  - Confounder, mediator, exposure, outcome ect…
- How will your measure them?
  - Detail the source of the data (be specific!)
- What is the validity and reliability of the measures?
- Explicit detail on how existing information is being used to define measure (e.g. algorithm, codes ect..)

Valid measurement

- Validity: Variable truly measures the domain
  - Not solely a property of the instrument, but rather the instrument in the particular research context
- Reliability: Precision, reproducibility
  - FFQ, radiologists rating scans ect..

Example: T2DM in the population



-Physiological state preceding diabetes

-Estimates of undx T2DM ~1/3
- Dependent on good and equitable screening

-Can have false +/-
-Various data sources to measure
-Can be biased to health-care users

-May be subject to error/bias

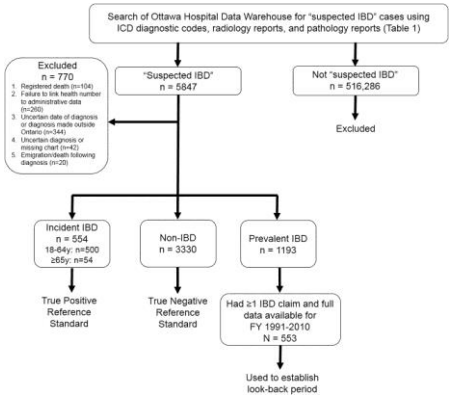


Fig. 1 Flow diagram of patients included and excluded in the algorithm development cohort derived from Ottawa Hospital Data Warehouse search. IBD, inflammatory bowel disease; FY, fiscal year.

Eric I. Benchimol , Astrid Guttmann , David R. Mack , Geoffrey C. Nguyen , John K. Marshall , James C. Gregor , Je...

Validation of international algorithms to identify adults with inflammatory bowel disease in health administrative data from Ontario, Canada

Journal of Clinical Epidemiology, Volume 67, Issue 8, 2014, 887 - 896

http://dx.doi.org/10.1016/j.jclinepi.2014.02.019

Create a variable table

Variable	Definition	Source	Form	Role	Validity
Neighbourhood educational attainment	% of population aged ≥15 years with high school education or less	Census	Percentage/ Proportion	Mediator	Aggregate/ Statistics Canada
Prior hospitalizations	# of hospitalizations in the past year	Canadian Discharge Abstract Database (DAD)	Count (0,1,2 ect.); Dichotomized at median (for e.g.)	Confounder	Cite CIHI-DAD validation studies
Asthma	Physician diagnosed asthma	OHIP/ NACRS/ DAD	Binomial (yes/no)	Outcome	Chart abstraction. 89% sensitivity &72% specificity (aged 0-17) and 84% sensitivity and 76% specificity in (aged 18+). Reference: Gershon A.S., et al. Canadian Respiratory Journal 2009; 16(6): 183-188

Examples

Variable	Definition	Source	Form	Role	Validity
Functional status limitation	Responding affirmatively to a survey question, "because of a condition or health problem, do you need the help of another person for: 1) preparing meals; 2) shopping for necessities; 3) doing normal housework; 4) doing heavy household chores; 5) personal care such as washing or dressing; or 6) moving about inside the house." No functional status limitation (i.e., none of the above)	Canadian Community Health Survey	yes (any limitation); no limitation	Exposure	Used in X,Y, Z studies; never formally validated (for e.g.)
Country of citizenship	Country of citizenship at time of landing	CIC database (1985 – 2010)	• India • China, • UK • Philippines • Pakistan • Other	Moderator	Maintained by Federal Government

Addressing threats to validity in the design

- Design is the first (and most important) step to maximizing the validity of a study
- In secondary data it is important to explore design options to minimize the major biases that can influence the study findings

Tools for addressing threats to validity in the design

- Design selection + enhancements
- Randomization (for primary studies)
- Restriction
- Matching

Example (Garg et al. BMJ 2012)

- Objective to determine whether people that donate a kidney have increased risk of CVD

P – Ontario population
I –Kidney donation
C –Compared to people who are non-donors
O – Cardiovascular Disease

Kidney donors are highly selected group (e.g. healthy) thus major possibility of confounding

Restriction

Living kidney donors who are permanent residents of Ontario
Index Date: Date of nephrectomy
(N = 2,028)

Since 1991

Looked for any condition that precluded kidney donation

Non-donors (with an OHIP card) are randomly assigned an index date

-Dx or procedure related to genitourinary disease, diabetes, hypertension, cancer, liver disease, rheumatological conditions, chronic infections, nephrology consult, frequent physician visits
-Also excluded those with no physician visits in 2 years prior

(Garg et al. BMJ 2012)

Restriction

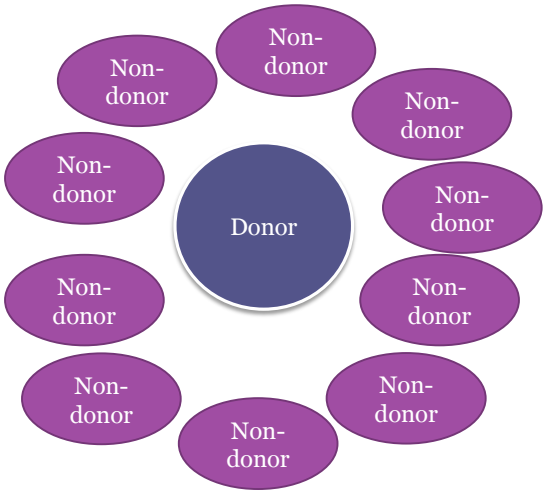
Non-donors (with an OHIP card) are randomly assigned an index date
(N = 9.6 million)

Excluded 85% because of prior conditions or no physician visit

Non-donors (N = 1.4 million)

(Garg et al. BMJ 2012)

Matching 1:10



Hard Match:
- Age (± 2 years)
- Sex
- Index date
- Rural/Urban
- Income quintile

(Garg et al. BMJ 2012)

Follow-up

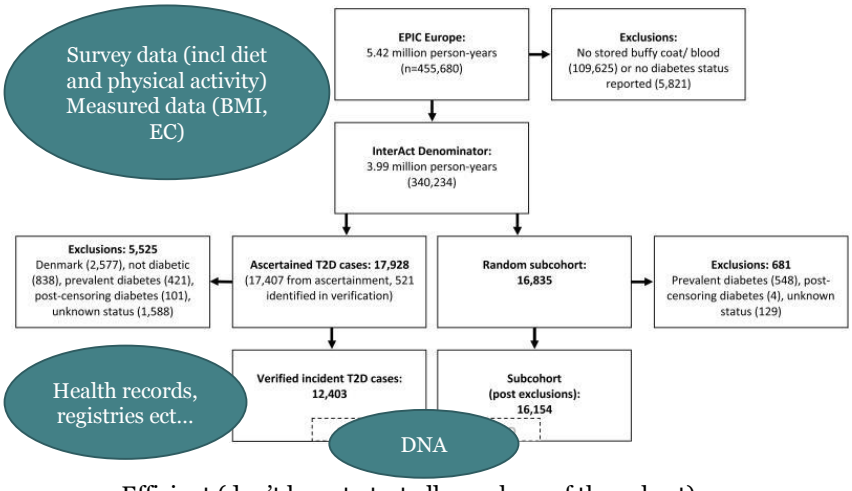
Donors

Age-sex-date-rurality-income matched and 'healthy' restricted controls

-March 31, 2010 or emigration or event (composite of death +CVD)

(Garg et al. BMJ 2012)

Case-cohort design and use of secondary data



-Efficient (don't have to test all members of the cohort)
-Analysis: Weighted Cox proportional hazards regression model

Claudia Lagenberg et al. 2014:11 (5) PLoS Medicine

Consider design alternatives + enhancements

- Case Crossover + Variations
- Negative Tracers
- Risk Periods
- Quasi-Experimental Design

Generalizaibility

- Tension between internal an external validity
- A study design can increase internal validity but decrease external generalizability
  - Don't maximize generalizibility without good rationale because it can affect internal validity
- One must decide on how far one can generalize results beyond the study population and ***how important this is to the research objective***

Study design & methodology tips

- **DETAIL**
  - Most critical part to a solid methods section is attention to detail regarding the approach
- Figures to outline design, recruitment, data collection, study popualtion are often helpful
- **Remember:** No statistics, no matter how fancy, can correct major flaws in design
  - This is a common fatal flaw on many grants

4. Analysis

- Clearly tie the analytic strategy to your:
  - Objectives
  - Hypothesis
  - Design
- Be clear about your variables and their forms
- Pay particular attention to data issues: i.e. clustered data, non-independence, repeat measures, latent variables, missing data ect…

If your are proposing to use regression, some questions to ask yourself:

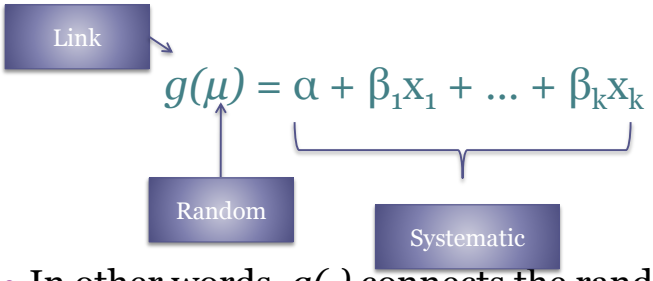
- What is the purpose of your model?
  - To obtain a valid estimate of an exposure-disease relationship
  - To obtain a good predictive model
  - To generate hypothesis about possible factors associated with your outcome
- The analytic steps differ depending what the purpose of the model

Analytic techniques

- Common (but not limited to) in health/epidemiology protocols:
  - Regression
    - Generalized linear models
    - Marginal and Mixed (random effect) models
  - Propensity matching
  - Instrumental Variable analysis

Generalized linear models

- The link function specifies a function $g(\cdot)$ that relates $\boldsymbol{\mu}$ to the linear predictor as



- In other words, $g(\cdot)$ connects the random and systematic components

Generalized linear models

Model	Dependent variable	Distribution	Link	Measure of effect
Linear $\mu = \alpha + \beta x$	Continuous	Normal	Identity	Beta
Logistic $\text{Log}(P/(1\text{-}P)) = \alpha + \beta x$	Binary	Binomial	Logit	Exp(beta) = Odds Ratio
Log-binomial $\text{Log}\ (P) = \alpha + \beta x$	Binary	Binomial	Log	Exp(beta) = Risk Ratio (RR), Prevalence Ratio (PR)
Poisson $\text{Log}\ \mu = \alpha + \beta x$	Count (or binary)	Poisson	Log	Exp(beta) = RR (also Rate Ratio with offset), PR
Log-linear-binomial $P = \alpha + \beta x$	Binary	Binomial	Identity	Beta = Risk Difference (RD), Prevalence Difference (PD)
Poisson $\mu = \alpha + \beta x$	Binary	Poisson	Identity	Beta = RD, PD
Negative Binomial $\text{Log}\ \mu = \alpha + \beta x$	Count (or binary)	Negative Binomial	Log	Exp(beta) = RR (also Rate Ratio with offset), PR

Marginal Models

- Applied to data with clustering or repeat observations
- Observations that cluster together are more alike than those that don't and **this results in invalid standard error estimates**
- When observations are not independent the information content of each observation is reduced

Generalized estimating equations (GEE)

- Specify a variance function and pairwise working correlation matrix to account for non-independence
- Does not affect the parameter estimates, but ensures the standard errors are more robust and appropriate
- Methodology covers the GLM family

Random effects or Mixed models

- Construct: Contains both fixed and random effects
- Types:
  - Random intercepts and random slopes
  - Multiple nested random effects
  - Multi-level models
    - Can have random effects with ecological or individual level fixed effects
- Generalized Linear Mixed Models (GLMM)

Specify a model building approach
Markers of a good model building approach

1. **Transparency:** Document which variables were considered
2. **Explicitness:** Be clear about which and why variables were considered and in final model model; leave nothing implied (ties back to conceptual model)
3. **Stay true to rules:** Be prepared to defend your choice of model and feel comfortable that your criteria were applied objectively
4. **Appropriateness:** Do you best to ensure your model building approach fits your research question/objective and data

5. Sample size

- Estimate of expected - or actual – sample size
- If using secondary data, the sample size should be known (or estimated)
- Use power calculations carefully – i.e. to test a specific hypothesis

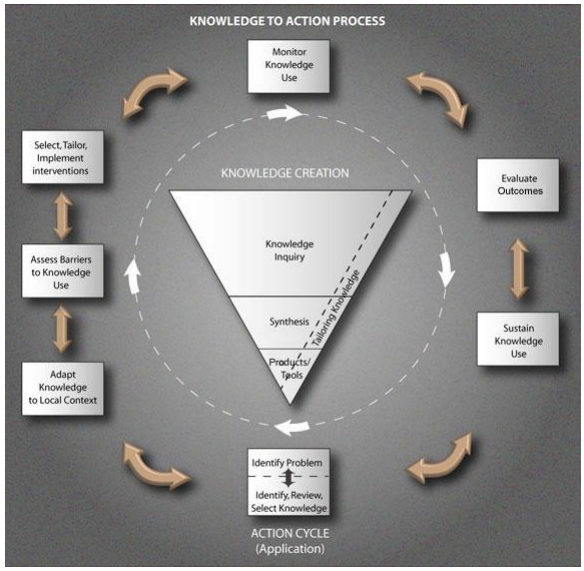
6. Ethics

- Protocol is needed for ethics application
- In a grant proposal - Be clear if ethics will be sought or add detail if it has been obtained
- Tackle any perceived thorny ethical issues head on

7. Knowledge translation/exchange

- Critical to demonstrate the creation of new knowledge and its translation into improved health
- Read CIHR material on KTE:

www.cihr-irsc.gc.ca/e/46986.html



Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, Robinson N. J Contin Educ Health Prof. 2006 Winter;26(1):13-24. Lost in knowledge translation: time for a map?

Types of KTE

1) End of Grant KT

- Make knowledge users aware of the knowledge that was gained during a project
- Typical dissemination and communication activities such as conference presentations and publications in peer-reviewed journals
- Other dissemination activities stakeholder events:
  - E.g. interactive educational sessions with patients/public, practitioners and/or policy makers, or media engagement
- Commercialization of scientific discoveries

2) Integrated KT

- Knowledge users are engaged in the entire research process (FROM THE START!)
- Researchers and knowledge users work together to shape the research including:
  - Determining the research questions, methodology, being involved in data collection and tools development, interpreting the findings, and helping disseminate the research results

Examples of Mechanisms and Knowledge Users

- Advisory committees
- Stakeholder events
- Training
- Use of knowledge broker

- Public health unit
- Government (e.g. Ministry of Health and Long Term Care)
- Health care practitioners
- Community organization

8. Timeline/feasibility

- Articulate the major activities, milestones and when they will be achieved
  - In certain funding applications, deliverables are tied to funding
- Without establishing feasibility, even a well written protocol will not get funded/approved
  - Can include data access, preliminary research, access to patients, existing agreements ect…

9. Research team environment

- Expertise and Environment
  - Leveraged resources
- Ensure appropriate methodological and content expertise is represented
- Related to establishing feasibility

10. Limitations and mitigation strategies

- Be sure to acknowledge all important limitations
- Acknowledging is not enough - think about **impact** and **mitigation**
  - Can argue why the impact is small
  - Can consider alternate analyses (sensitivity analyses/quantitative bias analyses)
  - Can refer to a future study or another research project

Sensitivity/Bias Analysis

- Lash: "Bias analysis estimate quantitatively the systematic error that remains after implementing a study design and analysis"
- Wherever possible in your protocol you should outline a plan for your sensitivity analysis
  - Determine the threats, plan how to assess

11. Significance and Impact

- Strong and articulate paragraph describing the impact of the research
- This is not a "throw-away" section
  - While this section may be given small weight/length – it can be what sets your proposal apart from others in a competition

Appendices

- Don't over-use them
- Don't put essential information there
- If you are applying for a grant – carefully read criteria on what is allowed in appendices

III. Overarching Tips for Success

- **Planning and preparation are critical**
  - Start early and get feedback
  - Consider a formal or mock peer review process
- If there are **evaluation criteria** – read them!
- **Be concise and precise**
- Outside of your protocol get as much **experience as possible reviewing protocols/grants**
  - Peer review panels
  - Offer to give feedback
  - Ethics boards

Want to discuss further?

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