What do you need to have in your application for HMRF?

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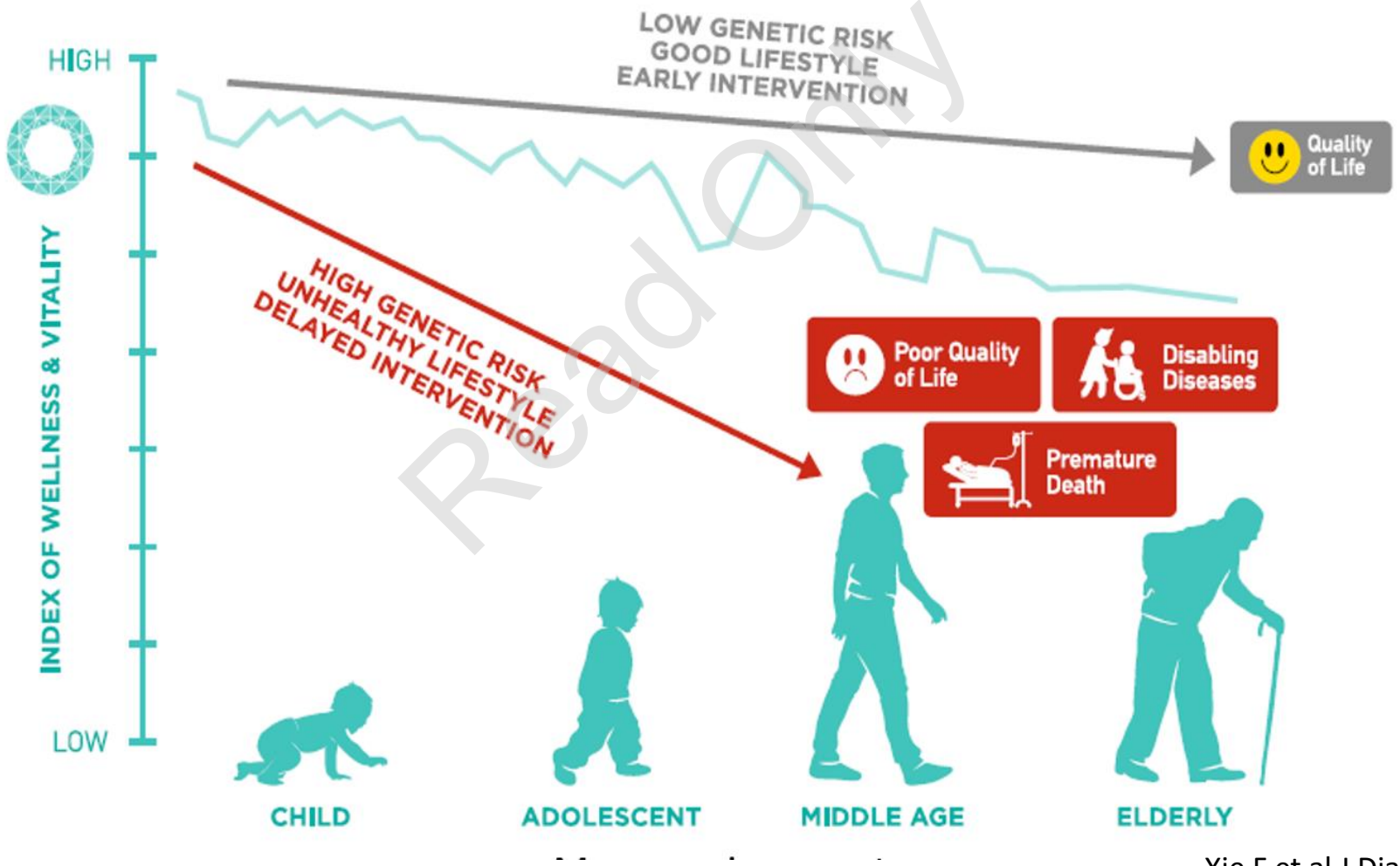
Declaration

- I am a physician researcher with accreditations in clinical pharmacology and endocrinology
- My research portfolio covers
  - Epidemiology, genetics, big data and multiomic analysis, clinical trials, implementation studies, real-world evidence related to diagnosis, prevention and treatment of diabetes and NCD
  - I work with colleagues, fellows and students in basic and data science
  - I am familiar with many of the challenges in translating evidence to clinical practice
- As a clinical pharmacologist, my primary interest is the relationship between drugs and human beings
- I design research protocol, conduct research and use research results to improve clinical outcomes

Multidimensional nature of human health and disease

Ancestry, Evolution, Ecosystem, Environment, Education, Economics
Culture, Cognition, Psychology, Behavior, Policies, Access



Xie F et al J Diabetes Investigation 2018

Health and medical research
Who are the stakeholders?

Beneficiaries/Patient
- What's wrong with me?
- Why should I have this problem?
- What will happen to me?
- Is the treatment safe and effective?

Care Providers
- What is the diagnosis?
- What is the cause?
- What is the prognosis (outcome)?
- What is the solution (therapy)?

Industry
- Diagnostics
- Devices
- Drugs
- Digital platform

Policymakers/Payors/Planners
- Return of investment (value)
- Evidence and cost-effectiveness
- Opportunity costs
- Short versus long term gain

Causes and consequences

One of the fundamental cognitive tasks in analytical thinking is to reason about causality. Thus one of the fundamental principles of analytical design is to show causality.

Austin Bradford Hill, “The Environment and Disease: Association or Causation?,” Proceedings of the Royal Society of Medicine, 58 (1965), 295-300.

https://www.edwardtufte.com/tufte/hill

Identifying problems and implementing evidence-based solution with impacts

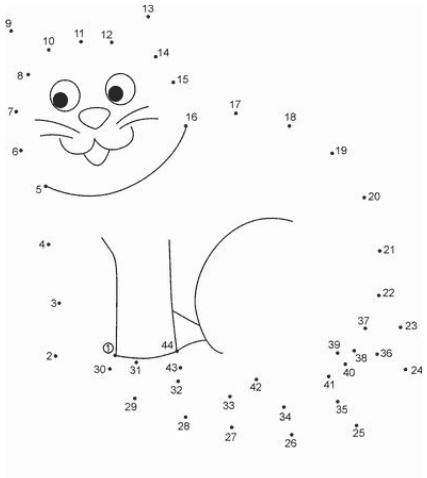
Defining the problem
- Epidemiology
- Prevalence and incidence
- Age/sex/ethnicity
- Heterogeneity
- Complexity
- Population stratification
- Mechanisms

Improving outcomes
- Physical, mental and social health
- Cognition, psychology, behavior
- Quality of life
- Work performance
- Functional capacity
- Hospitalization
- Morbidity and Mortality

Evidence for Solutions
- Health Promotion
- Disease Prevention
- Diagnosis
- Risk prediction
- Prevention
- Treatment
- Rehabilitation

Implementation – making a real difference
- Public-private-government partnership
- Technology and service delivery
- Investment
- Infrastructure
- Processes and logistics
- Human capacity

Observation, conceptualization, experimentation, practice



Clinical
Population

Experimental
Disease models

Observations

Associations
Inter-relationships

Concepts/Theory

Hypothesis

Observation (Epidemiology)
Cross sectional
Case control
prospective

Hypothesis

Experimental (Intervention)
Proof of concept
Uncontrolled
Controlled
RCT (single vs multi-centre)
Meta-analysis
Systematic review

Levels of evidence

Change dogma
Change guidelines

Change practice

Translational research
Outcome research

Change policy and system

Human experimental studies

- Prospectively assign human participants to conditions (i.e., experimentally manipulate independent variables)
- Assess biomedical or behavioral outcomes in humans for the purpose of understanding the fundamental aspects of phenomena
- Without specific application towards processes or products in mind

https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm

Clinical research

- Patient-oriented research
  - Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects.
  - It includes
    - mechanisms of human disease
    - therapeutic interventions
    - clinical trials
    - development of new technologies
  - It excludes ***in vitro*** studies that utilize human tissues that cannot be linked to a living individual
- Epidemiological and behavioral studies
- Outcomes research and health services research

https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm

Clinical Trials

- A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
- The term "**prospectively assigned**" refers to a **pre-defined** process (e.g., randomization) specified in an approved **protocol** that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo or other control) of the clinical trial.

What is an intervention ?

- A manipulation of the subject or subject's environment for the purpose of modifying one or more health-related processes and/or endpoints, e.g.
  - drugs/small molecules/compounds, biologics, devices
  - procedures (e.g., surgical techniques)
  - delivery systems (e.g., telemedicine, face-to-face)
  - strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits)
  - treatment, prevention, and diagnostic strategies.

https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm

Health-related biomedical or behavioral outcome

- **Pre-specified** effect of an intervention on the study subjects
  - Positive or negative changes to physiological or biological parameters, e.g.
    - improvement of lung capacity, gene expression
  - Psychological or neurodevelopmental parameters, e.g.
    - mood management intervention for smokers
    - reading comprehension and/or information retention)
  - Disease processes
  - Health-related behavior
  - Well-being or quality of life

https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm

Phases of clinical trials

- **Phase I.**
  - Tests a new biomedical intervention in a small group of people (e.g. **20-80**) for the first time to determine efficacy and evaluate safety (e.g., determine a **safe dosage range** and **identify side effects**).
- **Phase II.**
  - Study the biomedical or behavioral intervention in a larger group of people (**several hundred**) to determine **efficacy** and further evaluate **safety**.

https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm

Phases of clinical trials

- **Phase III**.
  - Study to determine **efficacy** of the biomedical or behavioral intervention in large groups of people (from **several hundred to several thousand**) by comparing the intervention to other standard or experimental interventions as well as to monitor **adverse effects**, and to collect information that will allow the interventions to be used **safely**.
- **Phase IV.**
  - Studies conducted after the intervention has been marketed. These studies are designed to **monitor the effectiveness** of the **approved intervention** in the general population and to collect information about any **adverse effects** associated with widespread use.

https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm

Writing a grant application = Story telling
Rationale - why do you want to know?

- What is the research question?
  - Diagnosis
    - signs, symptoms, lab, biomarkers, imaging, biopsies, algorithms…(vs gold reference)
  - Causation
    - genetic, lifecourse, environmental, biomedical, cognitive, psychosocial, behavioural .....
  - Prognosis/Outcome
    - functionality, quality of life, hospitalizations, disabilities, death..
  - Intervention
    - diagnostics, drugs, devices, digital, behavioural/policy/system change…

Writing a grant application = Story telling
Rationale - why do you want to know?

- What is the prior knowledge?
  - Yours and others (cite important work)
  - Originality of your work
  - Relevance of other work to local context (population, policies, practice)
  - **These work support your rationale to conduct the study**
- What is the research/knowledge gap?
- What is the expected outcome and impact?

Methods – how to close the knowledge gap?

- Hypothesis
  - supported by theory and plausibility
- Objectives
  - primary (use this to define sample size)
  - secondary
- Study design
  - Observational
    - Populations or cohorts (consecutive, random, predefined)
    - Cross-sectional, case control, prospective

Methods – how to close the knowledge gap?

- Study design
  - Experimental
    - Understanding disease mechanisms
    - Biomarkers (e.g. gene expression), physiological (e.g. insulin secretion)
  - Interventional
    - Quasi-experimental (pre and post evaluation)
    - Randomized controlled trial
    - Parallel or crossover or in waiting
    - Placebo controlled, active comparator
    - Multifactorial (combinations of interventions)
    - Single or multicentre

Predefined criteria, processes and outcomes

- Setting
  - community or clinic-based
- Inclusion and exclusion criteria
  - age, sex, ethnicity, socioeconomical status, co-existing conditions…
- Intervention and comparators
  - Placebo vs active drugs
  - Usual care vs intervention

Predefined criteria, processes and outcomes

- Outcome measures
  - Surrogate markers (e.g. change in BP, A1c, body weight, lipids)
  - Endpoints
    - e.g. MACE, heart failure, ESKD, death)
  - Patient reported outcome measures
    - e.g. depression, anxiety, QoL, health behaviors
- Cost-effectiveness analysis

Conduct of clinical trials

- Other confounders
  - TCM: multicomponent compounds, quality control, batch-to-batch variation and PK/PD data
  - Validity of questionnaires (Interviewers and interviewees)
  - Accuracy of diagnostics and devices
- Follow up procedures and measurements
- Personnel – who do what?

Conduct of clinical trials

- Sample size calculation
  - Refer to previous studies (if any)
  - Understand the epidemiology and causal relationship
  - Use mean and SD of the population to estimate variance and effect size of intervention
  - Large sample size for small effect size
  - Small sample size for large effect size
  - Effect size can be reduced as much as 50% just by participating in a trial
    - More attention, more measurement, more adherent, hawthorn effects, volunteer bias
  - Consult biostatistician

Clinical trials – making it happen

- 3R: Randomize, Record and Retain
- Attrition
  - Engage the trial participants, document contact details for tracking and recall
  - Complexity of trial procedures (e.g. no of visits, procedures, questionnaires)
- Do you have access to these patients or target population?
- Do you have the infrastructure and support to implement the study?
- Do you have clinicians to help recruit subjects if you are not a clinician?
- Do you have previous experience – have you done a pilot or feasibility study?
- Do you have collaborators and partners to help you deliver the study?

Clinical trials – making it happen

- Are the inclusion and exclusion criteria too strict?
  - More inclusive – more heterogeneity – larger sample size – more generalisable
  - Less inclusive – less heterogeneity – smaller sample size – less generalizable
- Estimate time needed to recruit subjects and achieve outcomes
- Estimate follow-up duration (first/last patient in, first/last patient out)
- Define the impact
  - Who are the beneficiaries
  - How can the results change practice, inform policy, capacity building
  - Publications, conference papers, training postgraduate students
  - Intellectual property
    - Novelty and utility with value
    - Patent, trademark, copyright, algorithms, logo, trade secret…

STROBE Checklist : Strengthening The Reporting of OBservational studies in Epidemiology

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

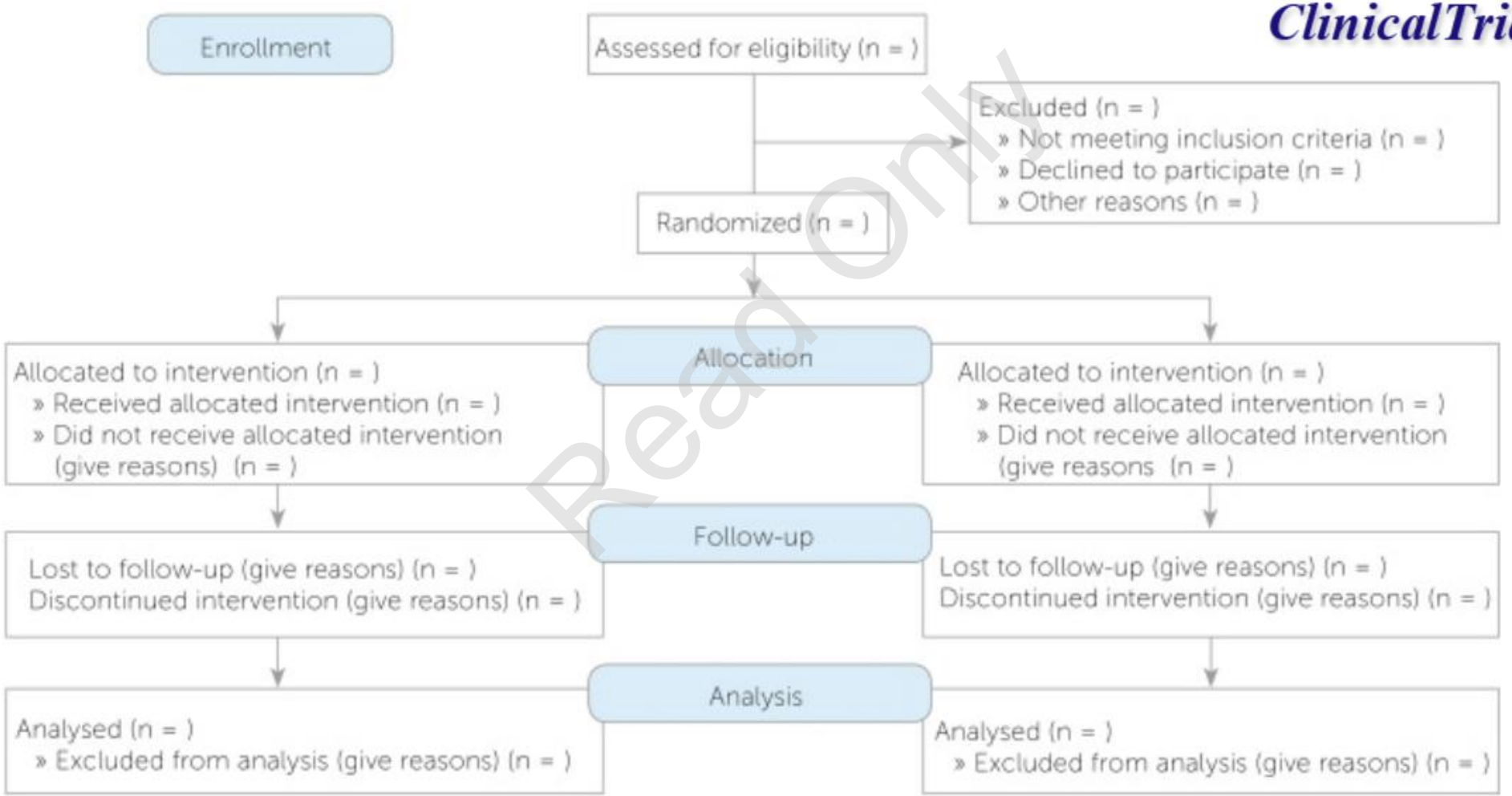
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

https://www.strobe-statement.org/checklists/

Consort Guideline for RCT and registering for a trial

NIH U.S. National Library of Medicine

ClinicalTrials.gov



https://www.equator-network.org/reporting-guidelines/consort/

Protocol, IRB, GCP and SOP

- Submit a full protocol with standard template including reporting of SAE and AE to IRB
- Familiarize and get certification for training in International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
- RCT aimed for government approval costs multi-millions of dollars
- HMRF-funded projects demonstrate proof of concept and feasibility for scaling up and provides opportunity to learn GCP

Protocol, IRB, GCP and SOP

- Conduct of study needs to comply with Standard of Operations (SOP) for
  - protecting safety of participants (written informed consent)
  - scientific merits
  - data integrity
- SOP pertinent to
  - Place, people, processes, ethical approval, financing, data collection, storage of database, investigational medicinal products (inventory, storage, disposal)….
- Consult the CUHK Clinical Research Management Office or HKU Clinical Trial Centre
- Consult Phase 1 Clinical Trial Centre at CUHK or HKU

Reviewer's perspective

- Most important: **ABSTRACT**
- Easy to read – logical, coherent and non-ambivalent
- No grammatical or typo errors
- Correct citations and reference list
- Flow charts, diagrams, timeline, milestones
- Track records – CV, prior publications and collaborations
- Realistic – under-budget for mega-projects
- Originality, feasibility, impacts
- Ask senior or other colleagues to go through it before submission
- If your supervisor can help you, read some successful applications

Cycle of scientific discovery, application and evaluation

Research is a humbling experience

Driven by curiosity and desire to understand and make a difference

The more you know the more you know you don’t know

Success is made up of many stories of failures

Impactful research takes time, efforts and luck

Good luck to all !