Clinical Study Design: From Pilot to Randomized Controlled Trials

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What is a clinical trial?

- NIH (2014): 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.
- http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html#sthash.3loKuSSu.dpuf

What is a Feasibility Study ?

- Pieces of research done before the pilot or main study
- Used to estimate important parameters that are needed to design the main study:
  - Standard deviation of the outcome needed to estimate sample size / statistical power;
  - Recruitment (study subjects and clinical sites), follow up rates, compliance;
  - ICC in cluster trials;
  - Follow up (attrition)
  - Compliance (As-Per-Protocol or Intention-To-Treat)

What is a Pilot Study ?

- A trial study carried out before a research design is finalized to assist in refining the research process or to test the components of the proposed study design.
- A small study to help design a further confirmatory study
  - refine the research methodology;
  - try out a procedure;
  - test of a principle or concept;
  - determine the safety of treatment or intervention
  - increase clinical experience
  - evaluate surrogate markers

Pilot or Feasibility Studies

- Early attempts to identify and adjust for unseen obstacles that could challenge the larger study
- The 'shakedown cruise of a new ship' to find out if all systems work as planned

- PubMed: 2554 Articles with 'Pilot Study' in the Title (2015)
- Clinical Trials . Gov: 506 Registered Trials with 'Pilot' in the Title (2015)

- As suggested by an African proverb from the Ashanti people in Ghana "You never test the depth of a river with both feet"

Pilot Study of RNS60 in Allergen-Induced Bronchoconstriction.

- RNS60 has demonstrated significant anti-inflammatory effects in several animal models.

- The goal of this study is to perform a mechanistic study showing regional improvements in inflammation and to better understand the physiology of such improvements.

- Positron emission tomography (PET) functional imaging will be used to determine whether RNS60 can attenuate allergen-induced eosinophilic inflammation in asthma.

- The study will use a blinded, crossover design where six patients will be treated with RNS60 and placebo for 21 days of each treatment. Baseline and post-treatment imaging will be analyzed to determine effect.

Pilot Study of Adjunctive Yoga for Bipolar Depression

- The primary aim is to develop a 10 week yoga program specifically tailored to bipolar depression.
- Develop an instructor manual for teaching classes and a scale for measuring instructor adherence to the manual.
- Evaluate the feasibility, acceptability to patients, and safety of this program in a 10 week pilot randomized controlled trial (RCT).
- Enroll 36 participants with bipolar I/II depression, and randomly assign them to either: 1) the yoga intervention, delivered as an adjunct to treatment as usual; or 2) treatment as usual enhanced with a publicly-available bipolar disorder self-help book (ETAU).
- Examine whether the yoga classes (compared to ETAU) appear promising in terms of reduced symptom severity and improved quality of life.

Studies without Pilot data (quick examples)

- Suicide Prevention
  - Over-estimated the incidence of the outcome – adaptive – changed endpoints
  - Over-estimated the recruitment – added civilians
- Vitamin D in Pregnancy
  - Incorrect assumption of recruitment – unfunded extension
  - Incorrect assumption of compliance – changed from intention to treat analysis to as per protocol analysis

Studies with Pilot data

- Recruitment plan to test new extubation protocol in NICU based on pilot study of historical incidence
- DSMC metrics established from high dose Vitamin D pilot

Thabane *et al. BMC Medical Research Methodology* 2010, **10**:1
http://www.biomedcentral.com/1471-2288/10/1

BMC Medical Research Methodology

COMMENTARY Open Access

A tutorial on pilot studies: the what, why and how

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Abstract

Pilot studies for phase III trials - which are comparative randomized trials designed to provide preliminary evidence on the clinical efficacy of a drug or intervention - are routinely performed in many clinical areas. Also commonly know as "feasibility" or "vanguard" studies, they are designed to assess the safety of treatment or interventions; to assess recruitment potential; to assess the feasibility of international collaboration or coordination for multicentre trials; to increase clinical experience with the study medication or intervention for the phase III trials. They are the best way to assess feasibility of a large, expensive full-scale study, and in fact are an almost essential pre-requisite. Conducting a pilot prior to the main study can enhance the likelihood of success of the main study and potentially help to avoid doomed main studies. The objective of this paper is to provide a detailed examination of the key aspects of pilot studies for phase III trials including: 1) the general reasons for conducting a pilot study; 2) the relationships between pilot studies, proof-of-concept studies, and adaptive designs; 3) the challenges of and mis-

Observational Studies (Quasi-experimental)

- Assignment of subjects is not performed by the investigator
- Subjects have 'self selected' their exposure and / or outcomes
- Careful attention to additional factors that distinguish the groups
- Confounders and Effect Modifiers
- Most Common
  - Cross sectional
  - Case Control
  - Cohort

Cross-Sectional Studies

- Examine data collected at a specific point in time.
- Usually from a population (not a sample)
- Provides estimates of prevalence

National Report on Human Exposure to Environmental Chemicals (CDC)

- Report 1: 2001, 27 chemicals, (NHANES 1999)
- Report 2: 2003, 116 chemicals, (NHANES 1999-2000)
- Report 3: 2005, 148 chemicals, (NHANES 2001-2002)
- Report 4: 2009, 212 chemicals, (NHANES 2003-2004)

Breastfeeding and obesity: Cross-sectional study. *British Medical Journal, 319*(7203), 147-150.

- In this study, researchers wanted to assess the prevalence of obesity among young children at the time of school entry and whether breastfeeding is associated with this status.
- Questionnaire data on children's breastfeeding histories and recorded the prevalence of overweight and obese children.
- No time-lapsed evaluation of specifically when children became obese and no control for other factors.

Case-Control Studies

- Subjects defined based on outcome
- Examines differences in exposures between those with the outcome (called cases) and those without the outcome (called controls)
- Cannot determine incidence rates
- Used when outcomes are rare
- Used with induction periods are long
- Caution when assessing exposure from recall, caution when outcomes are severe,
- Frequently first step in outbreak investigations

Outbreak Investigations

- 2000 Listeria outbreak: eating melons from a particular establishment and eating hummus from a particular establishment
- 2002 Salmonella outbreak: chicken and undercooked eggs

MMR vaccination and pervasive developmental disorders: A case-control study. *Lancet, 364*(9438):963-969.

- Examine the relationship between the MMR vaccination and autism or other pervasive developmental disorders (PDD).
- 1294 cases (subjects with the outcome of PDD) and 4469 controls (who do not have PDD) matched by age, sex, and health care provider.
- In studies that use subjects' recall memory rather than hospital records, there is the potential for recall bias, where the data collected may not be completely accurate.
- Odds ratio = 0.86 (95% CI: 0.68 – 1.09)

Cohort Studies

- Subjects defined based on exposures
- Examines differences in outcomes between exposed and non-exposed (called cohorts)
- Can determine incidence rates
- Used with outcomes are not rare
- Used with induction periods are relatively short (unless access to large data registries)

Cannabis use in adolescence and risk of future disability pension: a 39 year longitudinal cohort study. Drug and Alcohol Dependence 143:239-43

- Swedish longitudinal cohort
- 49,321 men born 1949-1951 and conscripted into military at age 18-20 years.
- Individuals who used cannabis more than 50 times in adolescence were 30% increased risk of disability pension from 40 to 59 years of age
- Controlled for social background, mental health, physical fitness, risky alcohol use, tobacco smoking and illicit drug use

Notable Cohort Studies

- British Doctor's Cohort Study
  - 35,000 physicians
  - Initially to explore high rates of lung cancer (cigarette smoking)
- Framingham Heart Study
  - 1948
  - Heart disease and high blood cholesterol
- Nurses Health Study
  - 1976 – 122,000 nurses
  - Long term consequences of oral contraceptives

Randomized Controlled Trials (Experimental Studies)

- Experimental Trials
  - Superiority
  - Non-inferiority / Equivalence

Special Types

- Cluster randomized
- Noninferiority / Equivalence
- Cluster randomized
- Play the winner
- Drop the loser
- N of 1
- Adaptive Designs (adaptive randomization, group sequential, sample size re-estimation, and more)

Adaptive Designs Resources

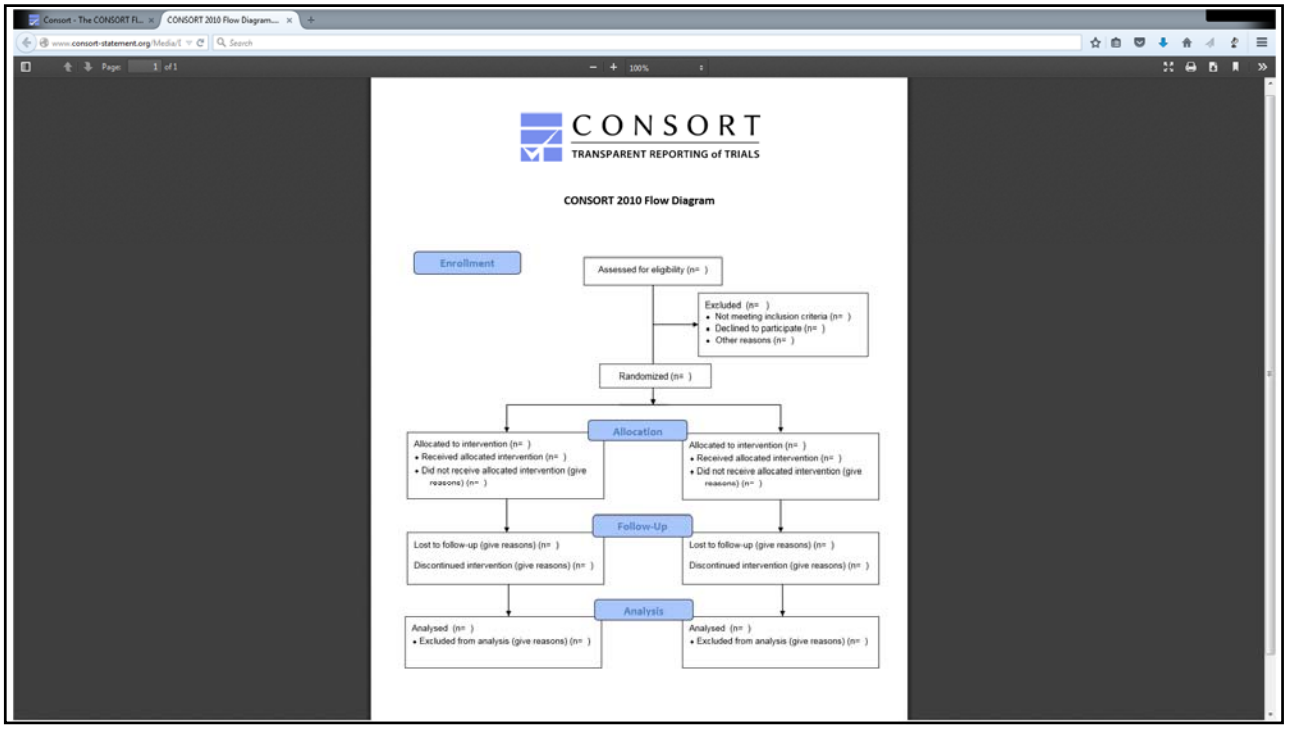
- Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics (FDA, 2010) 50 page guidance
- Adaptive design methods in clinical trials – a review. Orphanet Journal of Rare Diseases 3:11,1-13, 2008

CONSORT 2010: Consolidated Standards of Reporting Trials

- Minimum set of recommendations for reporting randomized trials
- 25 item checklist
- Flow diagram
- Extensions (such as noninferiority trials or cluster randomized trials)
- www.consort-statement.org

CONSORT Checklist (abbreviated)

- Title
- Abstract
- Background
- Objectives
- Trial Design
- Participants
- Study Setting
- Interventions
- Outcomes
- Sample Size
- Interim Analysis / Stop Rule
- Randomization
- Blinding
- Statistical Methods
- Participant Flow
- Losses and exclusions
- Recruitment
- Baseline Data
- Limitations
- Generalizability
- Registration
- Funding



STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

- Cohort studies
- Case-control
- Cross-sectional
- www.strobe-statement.org