Developing and Optimizing Clinical Trials When Conducting Delirium Research

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Disclosure

- Research funding:
  - NHLBI, NIA, AstraZeneca

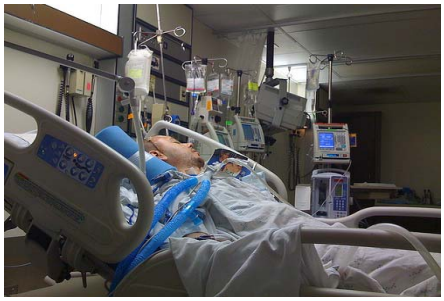
Outline

Study Protocol Considerations:

- Objective
- Design
- Sample
- Confounding variables
- Intervention
- Outcome(s)
- ~~Sample size~~
- ~~Data management and analysis~~
- DSMB

Study Implementation/Completion Considerations

Delirium



Pain

Agitation

Fear

Altered Sleep

ICU memories

Mobilization and Rehab

Chronic Pain

Depression

Return to Independence

Persistent Cognitive Defects

Reduced Functionality

Family stress

Mortality

Increased healthcare costs

Quality of Life

Background

- Delirium is a common sequelae of critical illness and worsens both ICU and post-ICU outcomes

Ouimet S. et al. Intens Care Med 2007; 33:66-73.
Ely EW et al. JAMA 2001; 78:221
Pandharipande P, et al. N Engl J Med 2014; 370:515-23.

Intensive Care Delirium Screening Checklist (ICDSC)

1. Altered level of consciousness
2. Inattention
3. Disorientation
4. Hallucinations
5. Psychomotor agitation or retardation
6. Inappropriate speech
7. Sleep/wake cycle disturbances
8. Symptom fluctuation

Delirium = ≥ 4 of 8 domains
- inattention must be present
Subsyndromal delirium = 1-3 of 8 domains
Neither Delirium nor SSD = 0 of 8 domains

- **An ICU patient who develops SSD (vs. a patient who develops neither SSD nor delirium) is more than 4x as likely to die in the ICU, spend more time in both the ICU and the hospital and be transferred to a SNF (vs. home)**

Bergeron N. et al. Intens Care Med 2001; 27:859-64.
Ouimet S et al. Intens Care Med 2007; 33:1007-13.

Role of Antipsychotics for Delirium Prevention in the ICU?

- Strong evidence to adopt non-pharmacologic strategies to prevent delirium in the ICU (e.g. early mobilization)

Schweickert WD, et al. *Lancet.* 2009;373:1874-1882.
Girard TD et al. Lancet 2008; 371:126-134
Kamdar B et al. Crit Care Med 2013; 41:800-9.

  - ***Will a pharmacologic delirium prevention strategy provide additional benefit?***

- Peri-operative antipsychotic administration may reduce delirium burden in non-critically ill populations

Prakanrattana U Anaesth Intens Care 2007; 35:714-19
Kaneko T, et al., Yonago Acta Med 1999; 42:179-84
Kalisvaart KJ et al. *J Am Geriatr Soc.* 2005;53:1658-66.
Larsen KA et al. Psychosomatics 2010;51:409-18
Hakim SH, et al. Anesthesiology 2012; 116:975-6
Wang W et al. Crit Care Med 2012; 40: 812-20

- One uncontrolled study suggests that ↑ haloperidol use over the course of the ICU stay may reduce delirium and mortality

van Boorgaard M, et al. Crit Care 2013; 17:R9

- However, two RCTs, suggest that use of haloperidol in critically ill patients (either with delirium or at high risk for delirium) does not influence patient outcome.

MENDS Girard TD et al. Crit Care Med 2010; 38:428-35.
HOPE-ICU Page VJ et al Lancet Respir Dis Aug 21 2013

Preventing ICU Subsyndromal Delirium Conversion to Delirium With Low-Dose IV Haloperidol: A Double-Blind, Placebo-Controlled Pilot Study

Nada S. Al-Qadheeb, PharmD, FCCP[1]; Yoanna Skrobik, MD[2]; Greg Schumaker, MD[3]; Manuel Pacheco, MD[4]; Russel Roberts, PharmD[5]; Robin Ruthazer, MPH[6]; John W Devlin, PharmD, FCCM[1,3]

NIA 1R15AG0349101A1

WWW.Clinicaltrials.gov #NCT01174290

Al-Qadheeb NS et al. Crit Care Med. 2016 Mar;44(3):583-91

Developing Great Clinical Research Questions

- *Ask interesting questions*:
  - Contemplate aspects of your practice:
    - Disconcerting patient outcomes?
    - Practice variability?
    - Conflicting or absent guideline recommendations?
  - Openly ponder and discuss your ideas with mentors/colleagues
  - Wait to conduct comprehensive literature reviews
- *Identify a good research question*:
  - Many interesting questions ≠ good research questions
  - Your initial question is likely too broad
    - Try to get to the "root" question by asking "why" repeatedly
  - What is the question's (effect) size, scope, scalability and sustainability?
  - It should fit the mission of both your institution and funding organization
- *Turn the research question into a testable hypothesis*:
  - A declarative sentence that predicts the results of a research study based on existing scientific knowledge and stated assumptions.

Hypothesis

- Administration of scheduled, low-dose, IV haloperidol in mechanically ventilated, critically ill adults with subsyndromal delirium will reduce conversion to delirium.

Defining the Study Objective(s)

- **Should include:**
  - an expression describing the overall approach
    - to assess, to compare, to determine
  - the patient population being evaluated **(P)**
  - a clear description of the intervention **(I)**
    - note: if medication should include dose, route and frequency
  - a clear description of the control **(C)**
  - the disease being evaluated
  - the general purpose of study
    - efficacy, safety, quality of life
  - the primary study outcome **(O)**
- **Limit the number of secondary objectives:**
  - Too many multiple comparisons will affect statistical rigor of study

Objective: To compare the efficacy and safety of scheduled low-dose haloperidol versus placebo for the prevention of delirium (Intensive Care Delirium Screening Checklist ≥ 4) administered to critically ill adults with subsyndromal delirium (Intensive Care Delirium Screening Checklist = 1–3).

Study Design

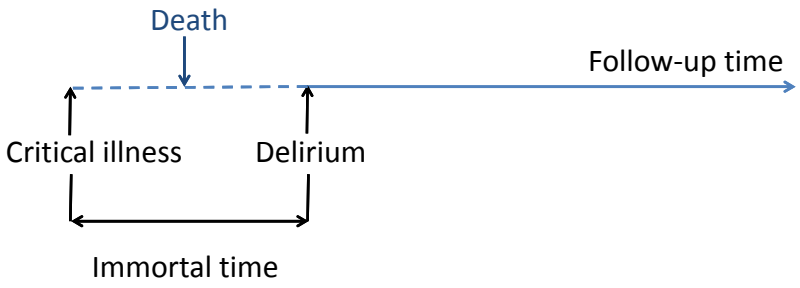
- Randomized
  - Only method to estimate causality
  - Best way to account for confounding and bias
  - Often suffers from poor external validity
  - Time consuming and costly to complete
- Cohort
  - Non-time dependent
  - Time - dependent

What about bias?

Systematic deviation in the variable of interest

Immortal time bias

- When a period of 'immortal time' is excluded



thebmj

BMJ 2014;349:g6652 doi: 10.1136/bmj.g6652 (Published 24 November 2014) Page 1 of 10

RESEARCH

The attributable mortality of delirium in critically ill patients: prospective cohort study

OPEN ACCESS

Peter M C Klein Klouwenberg *PhD student*[1], Irene J Zaal *PhD student*[1], Cristian Spitoni *statistician*[2], David S Y Ong *PhD student*[1], Arendina W van der Kooi *clinical technologist*[1], Marc J M Bonten *epidemiologist*[3], Arjen J C Slooter *neurologist-intensivist*[1], Olaf L Cremer *anaesthesiologist-intensivist*[1]

Table 2| **Effect estimates for association between delirium and mortality in intensive care unit using various statistical approaches**

Variables	Logistic regression	Competing risks survival regression	Marginal structural model
Adjustment factors:			
Baseline covariables	Yes	Yes	Yes
Time varying onset of delirium	No	Yes	Yes
Competing risks of death and discharge	No	Yes	Yes
Evolution of disease before delirium onset*	No	No	Yes
Effect estimate††:			
Crude	2.60 (1.76 to 3.85)	3.14 (2.32 to 5.04)	3.14 (2.32 to 5.04)§¶
Adjusted**	1.77 (1.15 to 2.72)	2.08 (1.40 to 3.09)	1.19 (0.75 to 1.89)†††‡

Study Sample

- **Who is your sample?**
  - This is your inclusion criteria
  - Single center vs. multi-center?
- **Pragmatism vs. control of confounding factors**
  - ↑exclusion criteria = ↓ external validity
- **Exclusion criteria**
  - IRB required (e.g., pregnancy, prisoner, consent not available)
  - Factors that could increase safety concerns
  - Factors that might confound ability to measure clinical response
    - This is most common reason external validity is low in many delirium studies
  - Consider a prior stratification at time of randomization to account for confounders
- **Use your DSMB as tool to influence an IRB that may be excessively "risk averse"**

TABLE 1. Study Exclusion Criteria

Age ≥ 85 yr
History of severe dementia (documented history and/or Informant Questionnaire on Cognitive Decline in the Elderly score ≥ 4) (30)
Acute neurologic injury primary reason for ICU admission
History of schizophrenia or a formal thought disorder
Antipsychotic use in the prior 30 d
Current treatment with a neuromuscular blocker or dexmedetomidine
Persistent use of deep sedation (Sedation Agitation Scale score ≤ 2) where daily awakening unlikely (26)
Acute alcohol or drug withdrawal
History of end-stage liver failure
QTc interval ≥ 500 ms (32)
Current drug therapy with a class Ia, Ic, or III antiarrhythmic (other than amiodarone)
History of haloperidol allergy
History of neuroleptic malignant syndrome
Recent cardiac surgery
Patients expected by attending physician to die within 24 hr
Patients expected by the attending physician to be discharged from the ICU within 24 hr
Inability to obtain informed consent
Pregnancy

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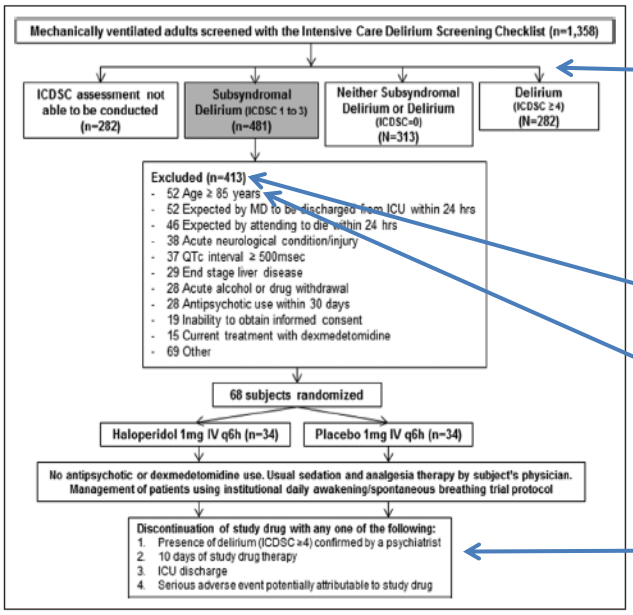

Figure 1. Patient screening, enrollment, and randomization. ICDSC = Intensive Care Delirium Screening Checklist.

All mechanically ventilated adults admitted to 3 different ICUs (medical n=2; surgical n=1) were evaluated q12h with SAS and the ICDSC for up to 3 days from the time of ICU admission:
- **Important way to reduce inclusion bias**

Among the 481 patients who had SSD only 68 were randomized = 14.1% !!

The Tufts MC IRB started off 'making us" exclude patients >/=80 years from trial
- DSMB helped get this up to 85 years

Important to carefully consider and define the criteria for stopping study intervention.

Anticipated safety concerns vs. Unanticipated safety concerns

Even in Smaller Pilot Studies, Randomization Usually Leads to Study Groups that are Similar at Baseline

	Haloperidol (n=34)	Placebo (n=34)
Age, yrs	61.7 ± 16.9	59.3 ± 14.9
Male, %	52.9	58.8
APACHE II, at study enrollment	19 [17-23]	20 [17-24]
ICU days before enrollment	1 [0-2]	1 [0-2]
IQCODE score	3 [3-3]	3 [3-3]
Pre-Deliric score, %	51 [36-75]	48 [38-71]
ICDSC score at study entry	2 [1-2]	2 [2-2]

Median [Interquartile range]
All differences p ≤ 0.05

If there is an important subgroup of patients who may respond to intervention differently: Incorporate stratification prior to randomization

If there is major potential confounding factor that could influence response to the intervention: A priori define a subgroup analysis to evaluate whether the primary outcome differs between the two different patient groups

Intervention(s)

- Need to carefully describe and justify:
  - Complexity? Based on PK/PD data?
- Placebo – controlled?
- Blinding?
  - Feasible?
  - Needs to be rigorous:
    - Bedside clinicians love to try to guess allocation!
- Who delivers/administers the intervention?
  - Research staff vs. bedside clinicians
    - If a clinician, cannot be too time consuming and must be within scope of practice
- Incorporate study medication into existing drug administration system.
- Control for use of confounding medications:
  - Non-study antipsychotics; dexmedetomidine

Should Delirium be the Primary Outcome?

Prevention of Delirium

- Incident delirium
- ICU days without delirium
- Time to first delirium episode
- Duration of first delirium episode

Treatment of Delirium

- Time to first resolution of delirium
- Duration of delirium
- ICU days without delirium
- Severity of the delirium

To most patients/families, an improvement in an outcome related to delirium is far more important than a change in the presence of delirium:

- Functionality/Quality of life
- Longer-term cognitive health
- Mortality

Neufeld KJ, et al. Am J Geriatr Psychiatry 2014; 22:1513
Yang FM, et al. BMC Med Research Method 2013; 13:8
Davis DHJ, et al. Am J Geriatr Psych 2013

Optimize the Rigor of Outcome Measurements

- ICSDC used in study ICUs for more than 10 years
- Bedside nurses receive formal didactic and bedside ICDSC re-education every 6 months
- ICDSC assessment was protocolized to occur after sedation DA
  - i.e., when patient maximally awake
- Additional delirium assessments encouraged
- All positive delirium assessments (ICDSC ≥ 4) were confirmed with a study investigator (using ICDSC) and a consultant psychiatrist using DSM-IV criteria

TABLE 3. Clinical Outcomes During Study Drug Administration

	Haloperidol ($n = 34$)	Placebo ($n = 34$)	p
Delirium, % (n)	35.3 (12)	23.5 (8)	0.287
Duration of first episode of delirium (d)	2 (1–2)	3 (2–4)	0.261
Proportion of 12-hr ICU nursing shifts without coma or delirium (%)	91 (67–100)	94 (80–100)	0.359
Proportion of 12-hr ICU nursing shifts without delirium (%)	100 (75–100)	100 (92–100)	0.236
Proportion of 12-hr ICU nursing shifts without coma (%)	100 (87–100)	100 (91–100)	0.708
Hours per study day spent agitated (Sedation Agitation Scale ≥ 5) (%)	0 (0–2)	2 (1–6)	0.008
Days where a continuous IV sedative administered (%)	95 (41–100)	82 (60–100)	0.666
Days where DA criteria met and DA completed (%)	100 (88–100)	100 (76–100)	0.667
Days where SBT criteria met and SBT completed (%)	100 (100–100)	100 (100–100)	0.499
Patients ever receiving early mobilization (%)	11.8 (4)	20.6 (7)	0.476
Dexmedetomidine exposure after randomization, % (n)	14.7 (5)	11.8	0.731
Exposure to nonstudy antipsychotic therapy, % (n)	0 (0)	0 (0)	1.000
Duration of first episode of subsyndromal delirium (d)	3 (2–4)	3 (2–5)	0.323

AQ15

DA = daily awakening, SBT = spontaneous breathing trial.
Reported as % (n) or median (interquartile range).

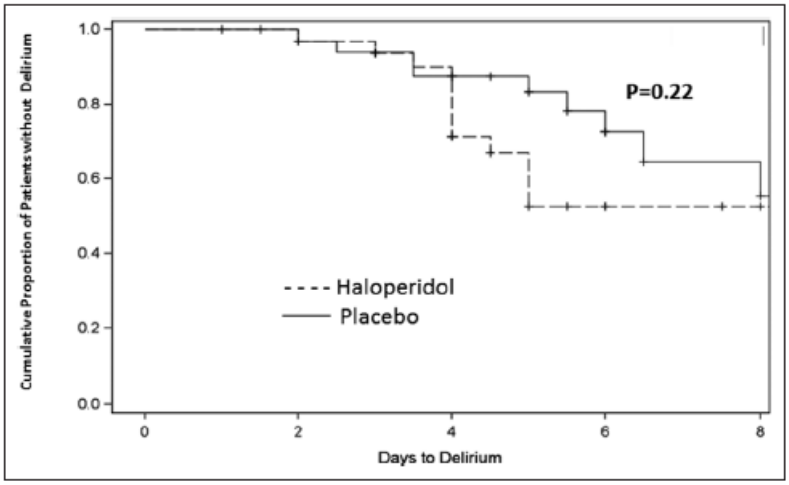

Figure 2. Kaplan-Meier plot for the time to the first occurrence of delirium between haloperidol and placebo groups.

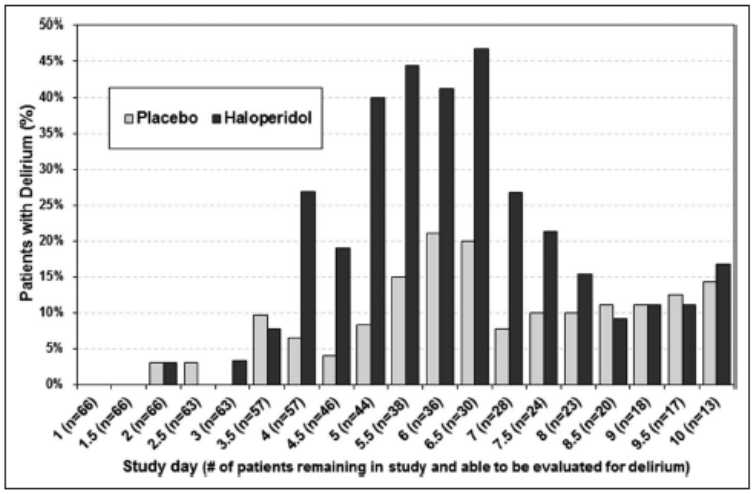

Figure 3. Presence of delirium on each study day between the haloperidol and placebo groups.

Special Considerations When Evaluating Safety

- Carefully protocolize the detection and management of expected safety outcomes:
  - Shows the IRB you are serious about safety
  - Delays/avoids removing a patient from the study
- Serious vs. non-serious adverse events
- Expected vs. unexpected adverse events
- Suspected Unexpected Serious Adverse Reactions (SUSAR)
  - An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Event/Reaction.
- Treatment allocation unblinding should be thoroughly discussed and should very rarely occur
  - If clinical team is unblinded, investigator blinding should be maintained

TABLE 5. Patients Where Study Medication Was Stopped Due to a Protocolized Haloperidol-Associated Event

	Haloperidol ($n = 34$)	Placebo ($n = 34$)	p
QTc interval prolongation, % (n)	11.8 (4)	2.9 (1)	0.16
Extrapyramidal symptoms, % (n)	2.9 (1)	0	0.31
Excessive sedation, % (n)	2.9 (1)	0	0.31
Hypotension, % (n)	2.9 (1)	2.9 (1)	1.00

Study Completion Considerations

- What's your "elevator" speech?
- Be rigorous about accounting for all patients screened
- Study implementation
  - Enroll a practice patient
  - Carefully validate all data collection forms
  - Ensure that all study procedures "fit" in with usual clinical care
- Informed consent
- Data collection
- Clinical team engagement
  - Continual education
  - Interact and update frequently
  - Reward good study compliance
- Patient and family engagement

Take Home Messages

- Developing a strong study objective takes time and should be enjoyed
- Balance pragmatism with rigor when defining the study population and design
- Study interventions should be well-justified and scalable
- Outcome(s) need to be valid, reliable and patient-focused
- Protocolize safety outcomes and their detection
- Motivate, educate and engage both research staff and the clinical team to ensure that research subjects are managed in both a compassionate and rigorous fashion