Grantsmanship: New Trial Design

Amy Abernethy, MD

Assistant Professor of Medicine and Nursing
Division of Medical Oncology, Department of Medicine
Duke University Medical Center
Durham, North Carolina, USA

Department of Palliative & Supportive Services, Division of Medicine
Flinders University & Repatriation General Hospital Daw Park
Adelaide, Australia

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Planning to Write a Grant

- *Before you begin:*
  - Talk with the program manager
  - Read, believe and follow the grant instructions
    - Font
    - Page limits
  - Find out how much money and the budget guidelines
  - Create a timeline for getting the grant prepared

Planning the Study

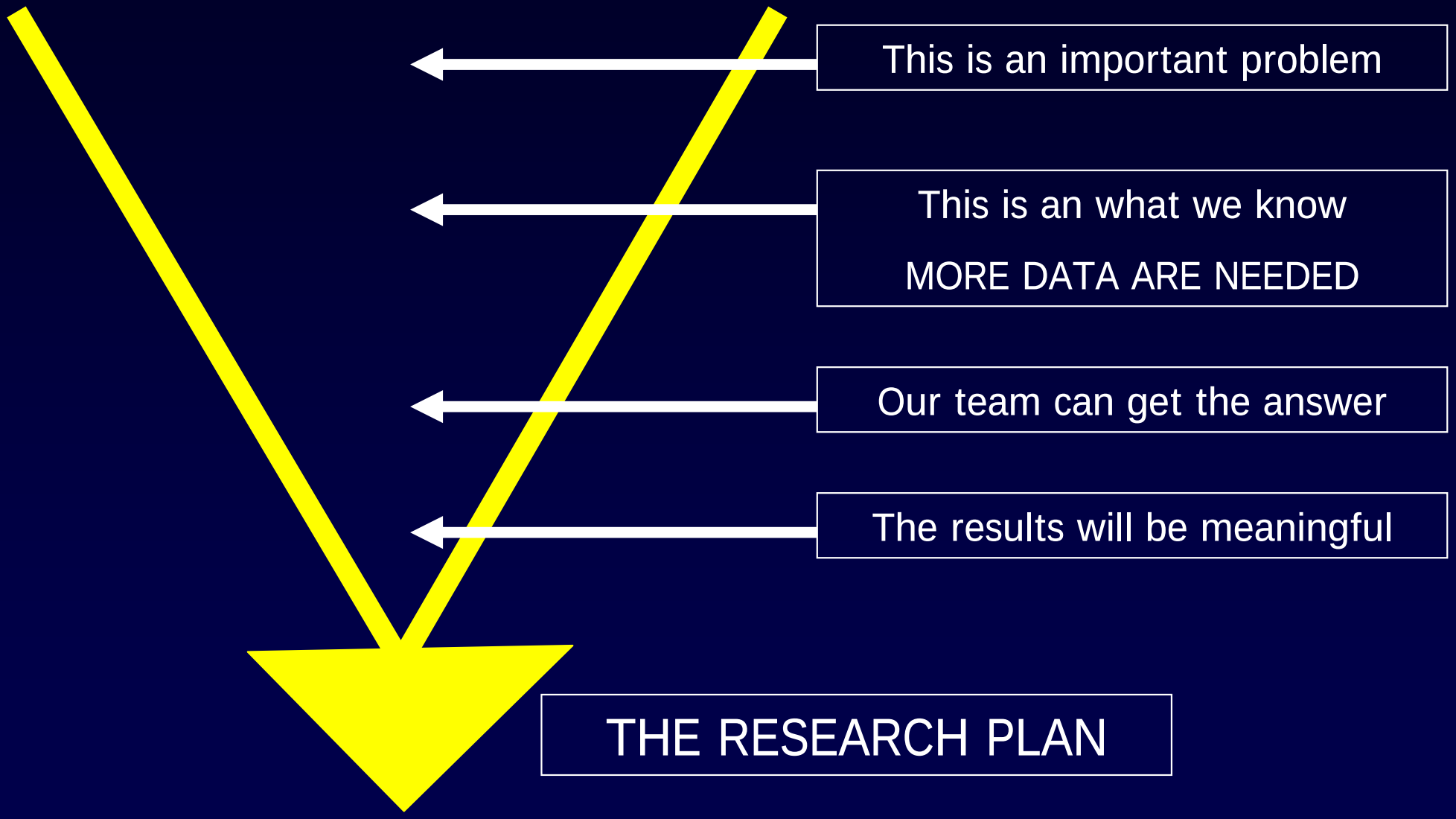
- *Sketch out:*
  - Specific Aims
    - Primary and secondary study objectives
    - Hypotheses to be tested
  - Background
    - Clinical and scientific context, rationale, prior evidence, and preliminary research
  - Your Preliminary studies
    - How have you contributed to this topic in the past?
    - What is your track record in this and other relevant areas?
    - Can your team work together?
  - SIGNIFICANCE
  - Research Plan

Tell a good story

Get the reviewers' attention!

Specific Aims page: THE TRAILER

Make it sparkle!



WELL, OF COURSE!

Put it in the expected order

Don’t make the reviewer work to figure it out!

Look at the grant instructions!

The Order

- Specific Aims
- Background, Significance, Preliminary Studies
- Research Plan
  - Overview of design & study diagram
  - Eligibility criteria
  - Setting
  - Procedures including recruitment, randomization/allocation, masking
  - Intervention
  - Measurements
  - Data management
  - Analysis plan & sample size
  - Ethical concerns
  - Pilot testing, study timeline and other items

Specific Aims

- Have clearly identified aims
- Primary and secondary
- Tangible, focused and doable
- Associated hypotheses to test

Specific Aims

Primary Aim:

To compare the effectiveness of oxygen versus medical air in relieving the sensation of breathlessness for patients with intractable dyspnea due to life-limiting illness in the setting of PaO_2>55mmHg.

Secondary Aims:

- To compare the effectiveness of oxygen versus medical air in improving QOL for patients with intractable dyspnea due to life-limiting illness in the setting of PaO2>55mmHg.
- To determine which palliative care patients benefit from oxygen, and the clinical characteristics that predict benefit.
- To document and compare side effects from oxygen versus air provided via nasal cannulae and concentrator.
- To document the costs of prolonged palliative oxygen therapy.

Primary Hypothesis:

Oxygen therapy is superior to air in relieving the sensation of breathlessness for patients with intractable dyspnea due to life-limiting illness in the setting of PaO_2>55mmHg.

Research Plan

Make sure that the research plan addresses the specific aims and research objectives

BE EXPLICIT!

Have clearly designed hypotheses, goals and approaches

Overview of Design

- Select the right kind of study design to match the study objectives
  - Quantitative or qualitative
  - Prospective or retrospective
  - Observational or experimental
  - Clinical trials designs
    - Different designs have various advantages and limitations
    - What is the control group?
    - Randomized?
    - Blinded/masked?
    - Single site or multiple sites?
- Must be doable

Palliative Care RCTs

- Randomized controlled trials (RCTs) = clinical experiments
  - designed to *reduce bias*
  - convincing evidence at 1st/2nd level of evidence hierarchy
  - *credible* to mainstream medicine and healthcare funders
- RCTs of both clinical interventions and health service interventions in palliative care are hard to conduct
- There are well-recognized pitfalls reported in the literature
  - systematic review

Barriers to Palliative Care RCTs

- Lack of research infrastructur
- Ethical Concerns
  - Research with vulnerable popu
  - Patient competence
  - Double agency
- Definition of palliative care
- Opposition to randomization
- Inability to achieve sample size goal
  - Recruitment difficulties
  - Attrition
  - Patient burden
- Outcome measures

Recruitment, recruitment, recruitment

Achieving sample size

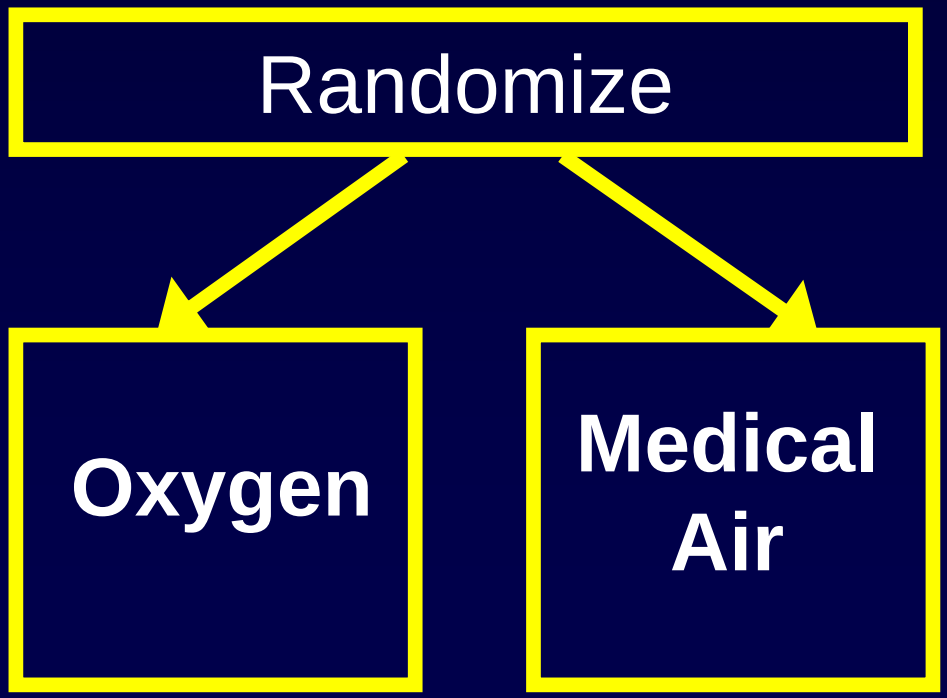
It must be doable!

Overview of Design

- Select the right kind of study design to match the study objectives
  - Must be doable
- Describe the study in basic terms
  - Readers must be able to follow what you are doing and why
- Include a study diagram

Examples: RCT

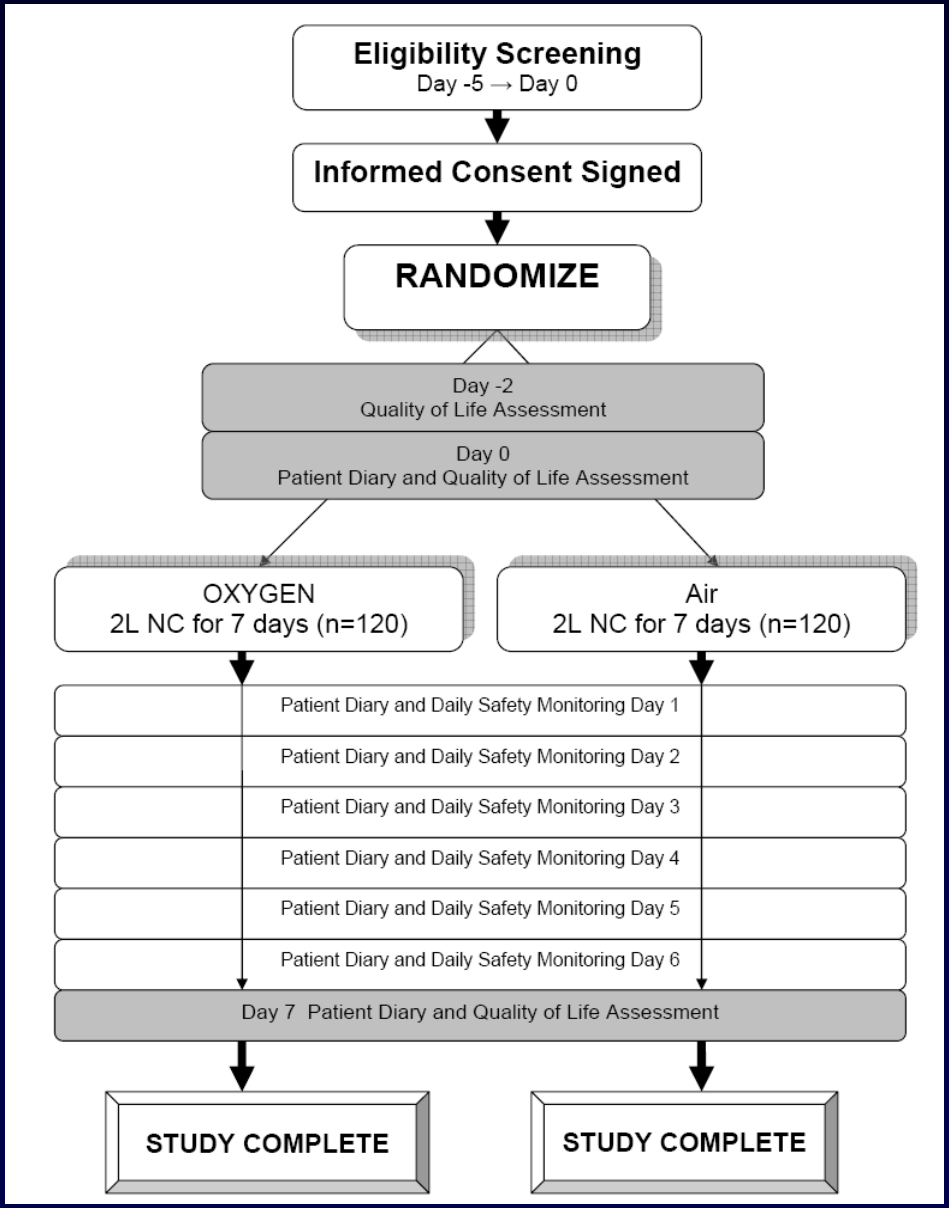
- *Palliative oxygen vs medical air for refractory dyspnea*
  - Parallel randomized, controlled, double-blinded design
  - Simpler to understand and execute
  - Accommodates disease progression
  - Large sample size requirement



Examples: RCT

Overview of Design: A multi-center, double-blind, randomized, controlled trial is planned (Figure 2). Eligible participants have intractable breathlessness at rest or with minimal exertion due to non-modifiable life-limiting illness but PaO_2>55mmHg; 240 participants are being recruited from seven sites in Australia, USA and UK. Randomization (1:1) is stratified by baseline PaO_2 and occurs through a central system executed by the oxygen company. Oxygen or medical air will be delivered continuously from identical appearing concentrators at 2 liters/minute through nasal cannulae for seven days; participants and investigators will be blinded to the gas provided. Outcome measures and analysis plans reflect the specific aims and the primary outcome is breathlessness on a 0-10 numerical rating scale (NRS).

Examples: RCT



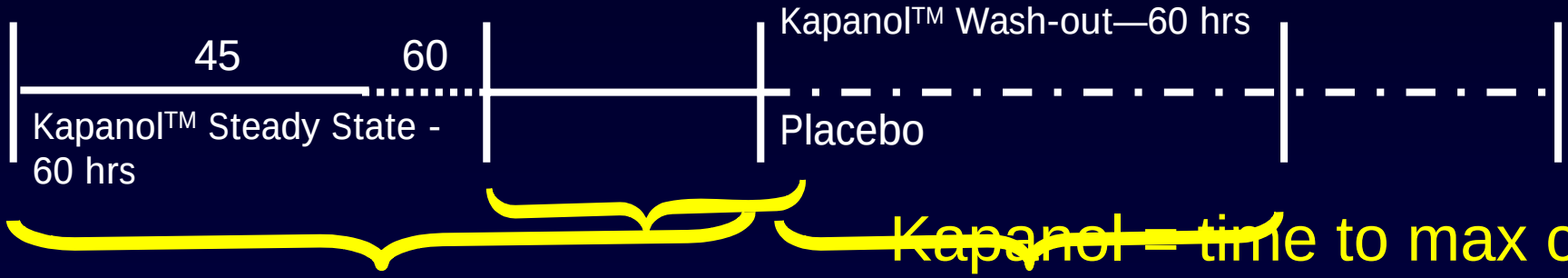
Examples: Cross-over Trial

- *Sustained-release morphine vs placebo for refractory dyspnea*
  - Randomized, controlled, double-blinded cross-over design
  - One half the sample size requirement of a parallel designed trial
  - Somewhat more difficult to understand and execute
  - Requires relatively stable disease over study period
  - Intervention must not be expected to have a differential effect if ordered intervention->placebo or placebo->intervention (sequence effect)
  - Intervention shouldn't have a differential effect by period (i.e., period 1 vs 2; period effect)
  - Need to allow adequate time in the design to accommodate wash out

Arm 1: Morphine followed by Placebo

Arm 2: Placebo followed by Morphine

Arm 1: Morphine followed by Placebo



Full placebo period

4 days (96 hrs)

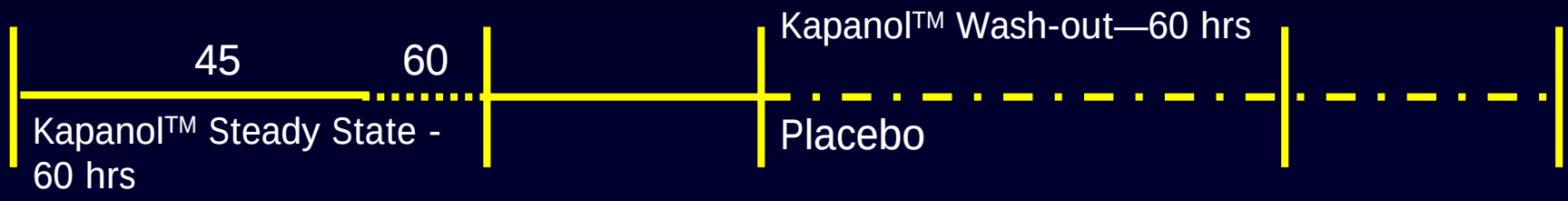
Full effect of drug

Kapanol = time to max conc is 9-12 hrs, therefore steady state at 45-60 hours

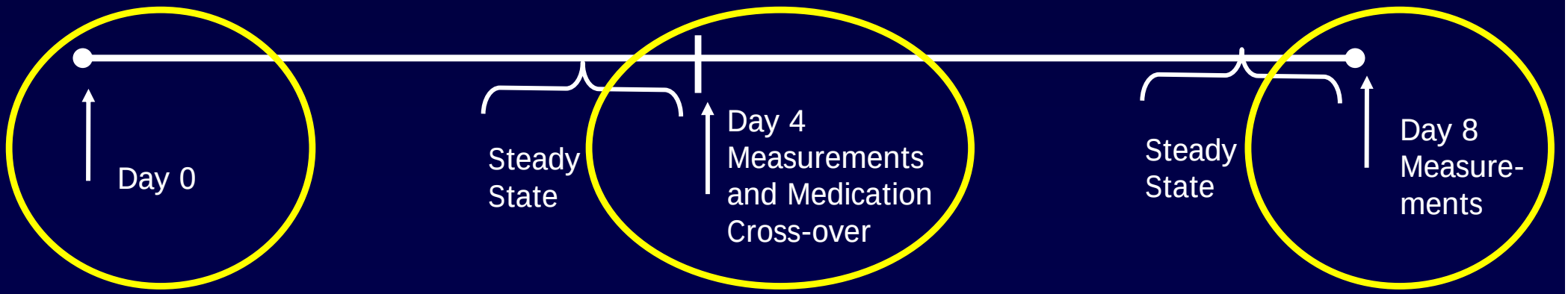
First 60 hours of the Arm 1 placebo period = wash-out

Arm 2: Placebo followed by Morphine

Arm 1: Morphine followed by Placebo



Arm 2: Placebo followed by Morphine



Examples: Factorial Trial

- *Case conferencing and educational interventions vs standard palliative care*
  - 2x2x2 factorial, controlled, cluster-randomized design
  - Substantially reduces sample size requirement because essentially tests all hypotheses with one sample
  - Much more difficult to understand and execute
  - Ability to test more than one intervention at once
  - Ability to test any interaction between interventions
  - Cost-effective
  - Can only be used when the two interventions are independent of each other

Example: 2x2x2 Factorial Trial

- **4 Hypotheses to test:**
  1. GP educational outreach visiting in palliative care pain management leads to decreased patient-reported pain intensity when compared to routine palliative care.
  2. Structured patient and caregiver educational outreach visiting in palliative care pain management leads to decreased patient-reported pain intensity when compared to routine palliative care.
  3. Case conferencing for patients requiring palliative care leads to increased time at an independent performance status compared to current routine palliative care.
  4. Whether there is any interaction between the interventions.

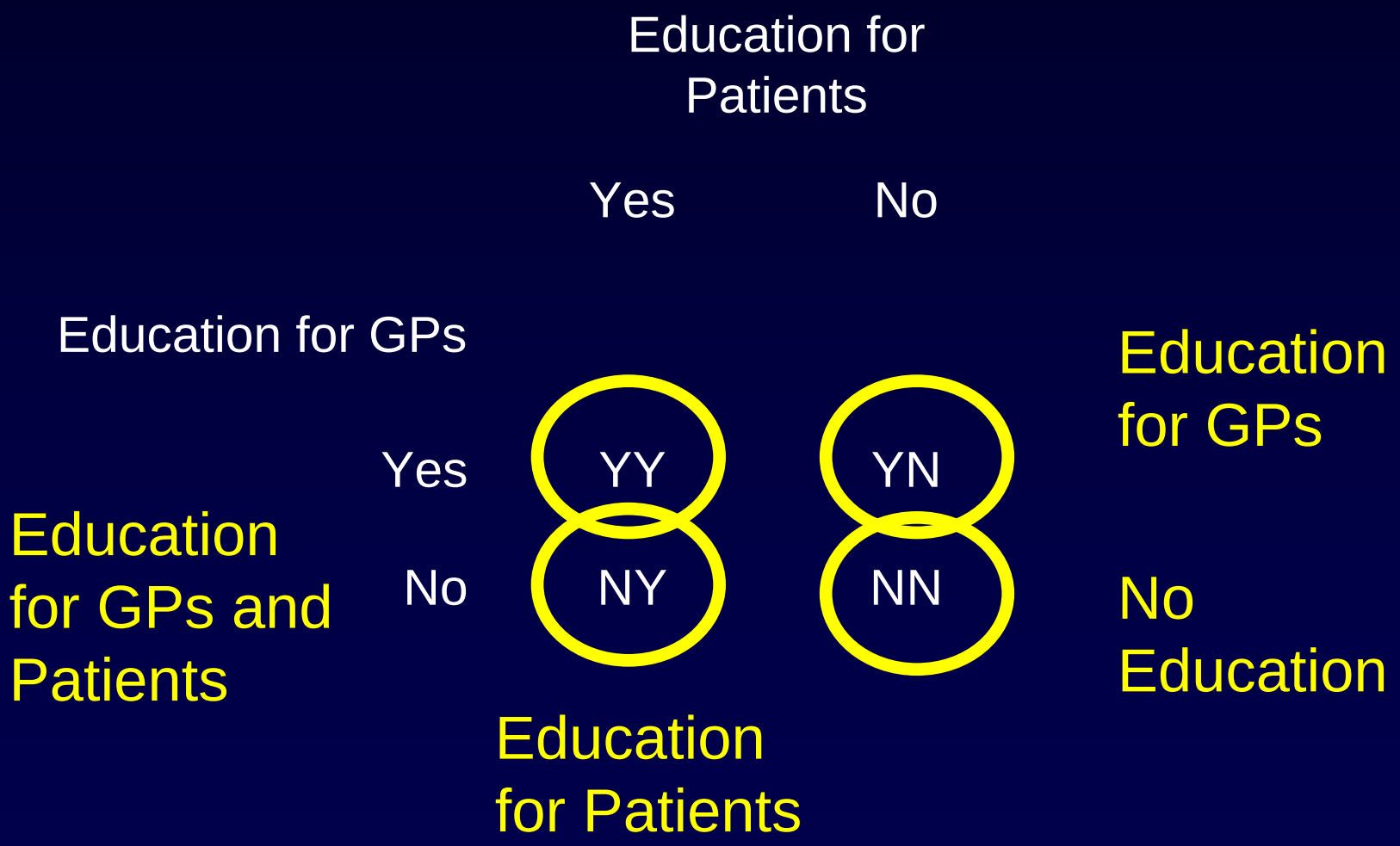
Example: 2x2x2 Factorial Trial

2x2 test of educational interventions

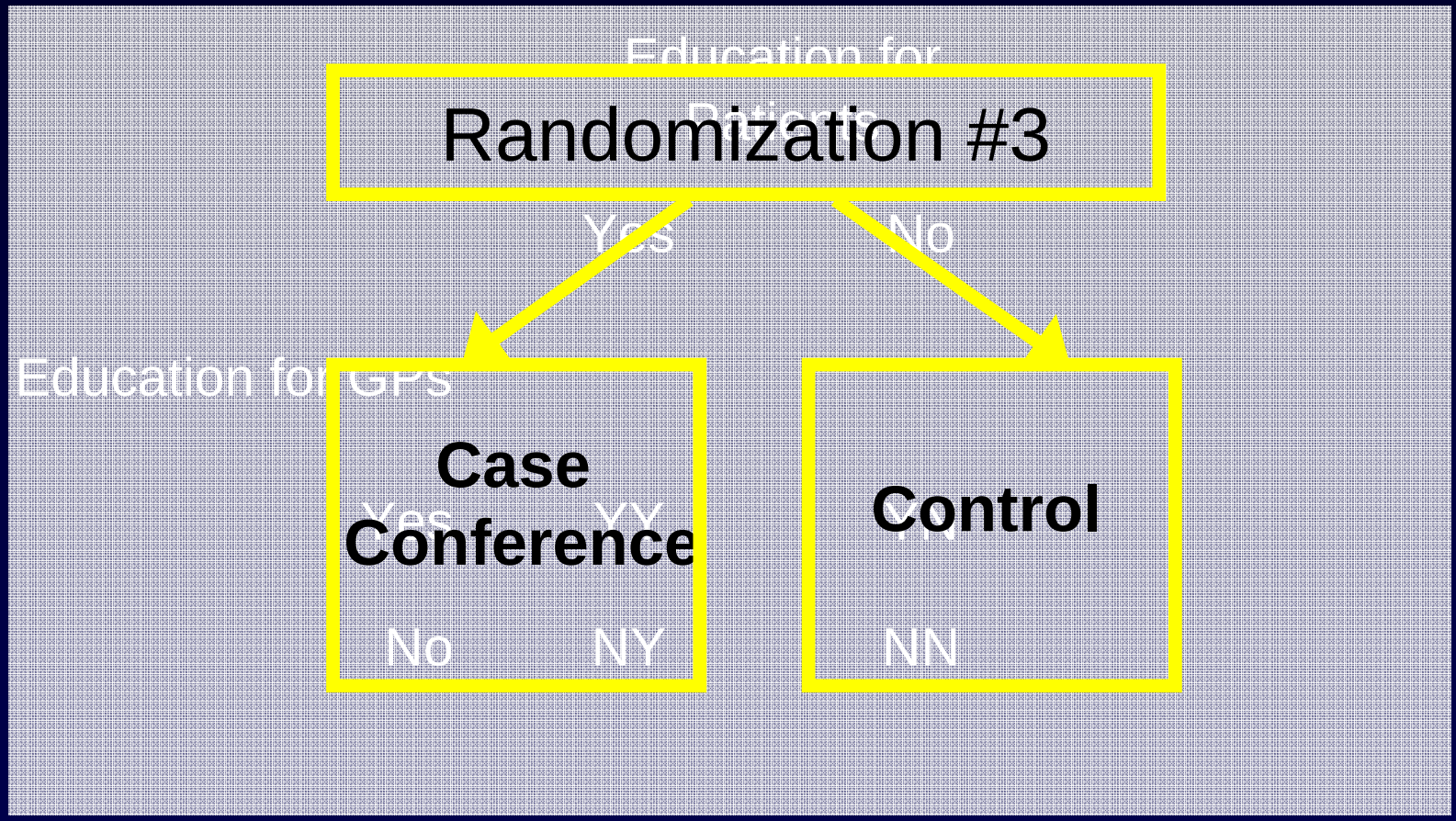
Randomizations 1 and 2 for Hypotheses 1 and 2

		Patient and caregiver educational outreach visiting	
		Yes	No
GP educational outreach visiting	Yes	Yes/Yes (GPs and Patients plus caregivers)	No/Yes (GPs only)
	No	Yes/No (Patients plus caregivers only)	No/No (Control)

Example: 2x2x2 Factorial Trial

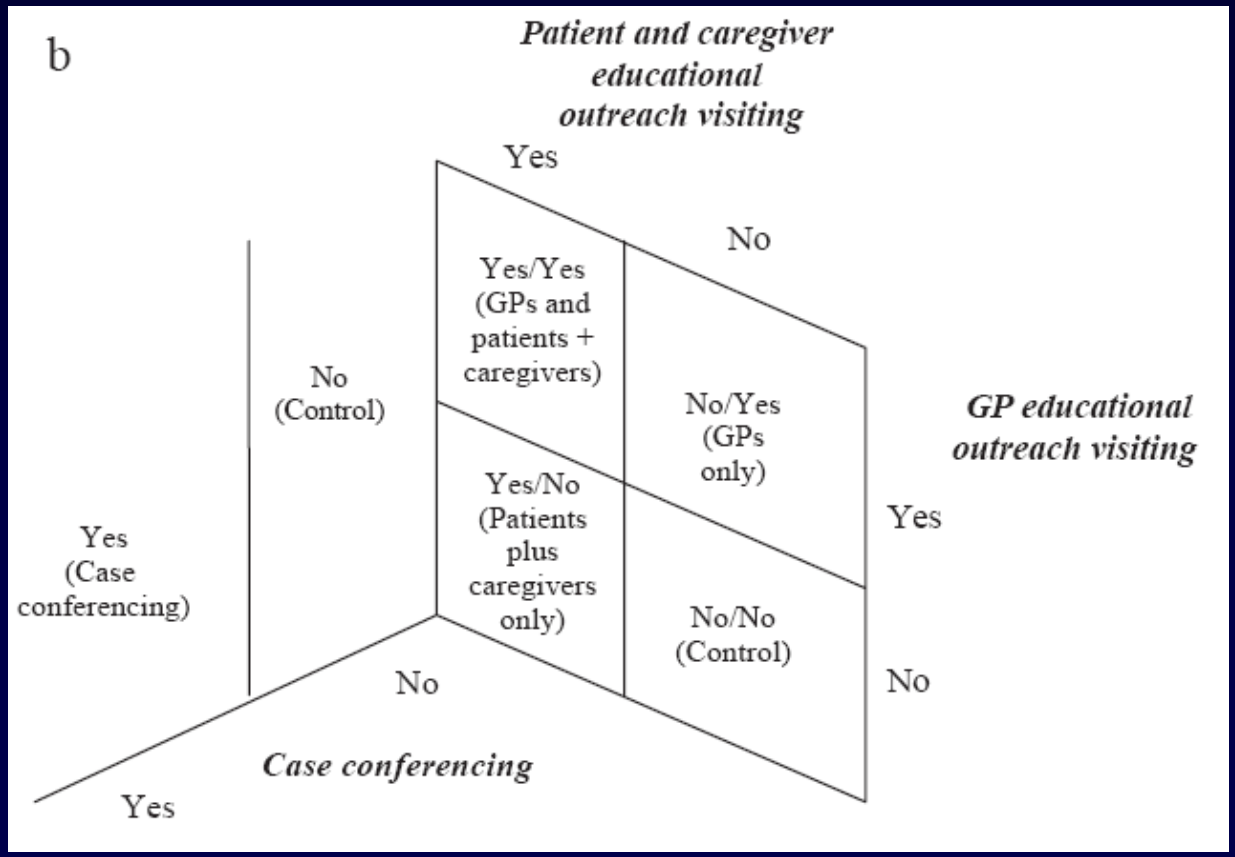


Example: 2x2x2 Factorial Trial



Example: 2x2x2 Factorial Trial

2x2x2 test of all 3 interventions in 3 dimension
Tests Hypotheses 1-4



Other Design Notes

- Adaptive designs
- Registration cohorts
- Historical controls
- Clustered designs
- Multiple research sites

- Etc. etc. etc.

Eligibility Criteria

- Inclusion criteria and exclusion criteria
- Broad vs narrow?
- Generalizability/effectiveness vs efficacy?
- Be very specific
- Be practical

Study Participants

Inclusion Criteria:

- Adult patients with intractable dyspnea and PaO_2>55mmHg in the setting of terminal illness where the underlying cause has been maximally treated. A medical specialist must document that all identified reversible causes of the dyspnea have been treated. PaO2 measurement must be in the last month.
- Dyspnea can be at rest or with minimal exertion, as measured by a score of ≥ 3 on the Medical Research Council categorical dyspnea exertion scale.
- On stable medications over the prior week except routine "as needed" medications.
- Prognosis of at least 1 month in the opinion of the treating physician.

Exclusion Criteria:

- Meets international guidelines for long-term oxygen therapy with PaO_2 56-59mmHg, i.e. symptomatic pulmonary hypertension with cor pulmonale.
- Hemoglobin<10.0g/dL as measured within one month of baseline evaluation.
- $PaCO_2$ >50 mm Hg.
- Confusion with Folstein Mini-mental Status Exam <24/30.
- Current oxygen therapy or continuous oxygen therapy in previous week.
- Actively smoking.
- Active respiratory or cardiac event in the previous 2 weeks, not including upper respiratory tract infections. Illness must be resolved for at least 2 weeks prior to baseline evaluation, as judged by a doctor involved in the care of the patient.
- Previous respiratory failure induced by oxygen.
- Unable to give informed consent or complete diary entries.

Setting

- A clear description of where the study will take place
- One site or many sites
- Critical for generalizability
- Palliative care clinical trials specifically:
  - Type of program
  - Funding
  - Disease profile
  - Length of stay
  - Provider profile and referral patterns

Study setting (Oxygen study). Participants will be recruited through the palliative care, oncology, respiratory, cardiology, and general medicine departments at five sites in Australia, one site in the USA, and two sites in the UK. These sites have all been extensively described in the Research Resources sections. These settings were chosen because they represent three healthcare systems and five different configurations for palliative care service delivery.

Study setting (Palliative Care Trial). The trial was set in Adelaide, South Australia. Participants were recruited from Southern Adelaide Palliative Services, an interdisciplinary specialized palliative care service serving a population of 350,000. The service supports local GPs; GPs provide the majority of primary and palliative care to patients with life-limiting illnesses in Australia. Staff includes specialist nurses, palliative medicine physicians, social work, bereavement, complementary care, and volunteers. In addition, the palliative care service interfaces with other local healthcare support services such as home nursing, physical therapy, hospitals, and nursing homes. The palliative care service has acute inpatient, inpatient consultative, and hospice functions, and sub-acute respite and outpatient functions. The delivery of palliative care in southern Adelaide is consistent with the definition provided in the United States (US) National Consensus Project definition and recommendation for quality palliative care.

Study Procedures

- Clearly detail how things are going to happen
- Recruitment – *NEED TO BE VERY SPECIFIC*
  - Screening
  - Consent
  - Feasibility and piloting
  - Quality assurance
- Randomization / allocation
  - Randomization method
  - Stratification
  - How are assignments made and who will do this?
  - How will assignments be applied?
- Masking
  - How will participants, clinicians and investigators be blinded?
  - What will happen if a participant needs to be unblinded?

This section shows the grant reviewers you know what you are doing

C.3.1 The parallel randomized design pilot: ***EVIDENCE OF A FEASIBLE STUDY DESIGN AND RECRUITMENT TECHNIQUE***

Clearly the ideal study design is a parallel randomized controlled trial design testing oxygen versus medical air in the study population of interest. In 2003, our Australian team (including Abernethy) was awarded NHMRC funds for the study design described in this application. This grant would only fund a proportion of the Australian participants to be recruited to the full trial. Given feedback from reviewers, we elected to use this money to complete all preliminary planning (e.g., data forms, data management system) and test recruitment strategies. Study management items are described in Section D. The study was conducted exactly as described in this application, focusing on the Adelaide, Australia (Flinders University) and North Carolina (Duke University) sites first. Main objectives focused on recruitment feasibility and baseline demographics and outcomes. Once effective recruitment techniques were consolidated in Adelaide, the Melbourne (Austin Health) and Sydney (Royal Prince Alfred) sites were incorporated into the pilot. Tasmania obtained independent funding and has also proceeded. The model is amended slightly at each site, and all modifications are documented.

Recruitment programs at the Adelaide and North Carolina sites were modeled after the recruitment program of the Palliative Care Trial. First, the site Clinical Research Nurse who already had palliative care experience was trained in communications, research ethics, and social marketing. Key messages for the recruitment visit and associated diagrams detailing the study have been developed. Recruitment visits are periodically role-played including reviewing the consent documents to ensure quality and repeatability. The site PI has interface with local stakeholders (e.g. pulmonologists, oncologists, palliative care teams) to generate interest and buy-in.

A case-finding method for each site consistent with local privacy laws and Ethics Committee / IRB requirements was developed. In general, the Flinders system has been most successful. The Clinical Research Nurse visits outpatient clinics during periods when eligible patients are most likely to have appointments (e.g. high COPD patient volume). She has a group of pre-printed information sheets about the trial (Appendix G.1) which she distributes to clinicians periodically during clinic hours. She is available for discussions with clinicians, but does not interact with the patient until express consent is provided by the patient through the clinician (in accordance with Australian Privacy Law). In the US, IRB permission for Review Preparatory for Research permits case finding, but the clinic-based model is still most effective. This model is now being transferred to the Sydney and Melbourne sites.

During the recruitment visit, the Clinical Research Nurse reviews the consent documents in full. She answers questions and provides the potential participant (and his family) space to make a considered decision. All consent documents are maintained and stored in accordance with local ethics requirements. Copies of all documents are filed in the study notebook according to the Standard Operating Procedure.

Clinical Research Nurses prepare weekly recruitment logs (Appendix G.2) that are forwarded to the coordinating site. These logs enhance recruitment by highlighting site-based concerns early. The Continental Clinical Research Manager oversees the site recording to ensure that data is of highest quality. Key Performance Indictors (KPIs) are monitored monthly (Appendix F.1 and Table 2); numbers for the KPI reports are generated from the site weekly logs. Experience from the Palliative Care Trial suggests that KPIs alert the team to systematic recruitment concerns and other feasibility problems. Monthly site and total graphs will be sent to site investigators during the main trial to enhance the monitoring system.

Randomization and Masking

Consenting participants will be randomized 1:1 to oxygen versus medical air, stratified by PaO_2 ($Pa0_2$ <70, $Pa0_2$ 71-80, $Pa0_2$ 81-90, $Pa0_2$ 91-100). Randomization is in balanced blocks of 4 within each strata based on the Fisher and Yates Statistical Tables. A set of randomization codes sealed in individual opaque envelopes will be prepared for each site and sent to the oxygen company. Each company receives 4 boxes of envelopes corresponding to the 4 strata. After consent, the site Clinical Research Nurse tells the oxygen company designate into which strata the participant fits. The oxygen company designate then selects the next envelope in the box marked with the corresponding strata designation. The card in the envelope indicates the intervention allocation – oxygen or air. The oxygen supply company will then record the Participant Identification Number (PIN), randomization number on the envelope, strata, and allocation assignment on a prepared log that is maintained at the oxygen company. Only the oxygen company and the randomization service will be aware of the assignment unless unmasking is required for medical or ethical reasons. Identical concentrators will be used and the assignment will be concealed from study investigators and participants until the end of the study.

Intervention

- Clearly describe the intervention and control
  - Be very specific about all elements
  - What exactly does it entail?
  - How long will the intervention last?
  - What is the quality assurance plan?
  - How will you ensure that the same intervention is delivered across all sites?
  - Are there any issues with compliance?
  - Are there any specific modifications to meet the needs of people with life-limiting illness?

Intervention

Participants will receive oxygen or air delivered at 2 liters per minute via concentrator and nasal cannulae for 7 days. Participants are expected to use the therapy for more than 15 hours per day. Local oxygen companies have been contracted to provide the therapy; oxygen concentrators will be specially modified to deliver air using a technique with molded rubber designed by Bob Wyatt at WyMedical in South Australia. Each site organizes a teleconference between the local oxygen company and Mr. Wyatt to ensure that the methodology is conveyed appropriately. Concentrator meters will provide evidence of gas delivery. Spot concentrator checks will be documented at least monthly to ensure quality.

Concentrators will be delivered on the morning of Day 0 and retrieved on the morning of Day 7. The company will deliver the concentrator to the patient by 09:00 am on the arranged day, the patient will have been completing the first 2 days of the study diary. The company will deliver the concentrator directly into the patient's home. On delivery, the person trained specifically to deliver the concentrator will follow a "Delivery Script" to ensure that the blinding is not compromised.

In order to ensure intervention quality, trial investigators and the oxygen company will agree in writing to an explicit set of oxygen company responsibilities. Oxygen companies must prepare the modified concentrators according to Bob Wyatt's scheme. The company must adhere to all of the rules regarding randomization including not revealing the allocation assignment, safekeeping of the allocation codes, and being available 24-hours daily for emergent unmasking if needed. Document companies will provide timely drop-off and pick-up of oxygen concentrators, and document meter readings at both times.

Measurements

- Clearly describe the methods of measuring impact of the intervention
  - What are the measurement instruments?
  - What is the frequency of measurement?
    - Present this on the study diagram
  - What is rationale for choosing each measure?
  - Is the measure valid? In your population?
  - How exactly will the measure be conducted?
    - Surveys/questionnaires
    - Blood tests and laboratory studies
    - Functional tests
    - Interviews
  - What is the quality control plan?
  - Have you considered & addressed respondent burden?

This section shows the grant reviewers you know the science

And that you can find references

Measurements (part of the section)

Descriptors of breathlessness help to characterize the experience. Cluster analysis can predict etiology of breathlessness. The utility and meaning of these descriptors and their clusters have been demonstrated for people with advanced cancer and breathlessness by Wilcock and colleagues. The fifteen categorical descriptors will be presented to participants in random order during baseline assessment. Patients will be instructed to choose any number of descriptors appropriate to characterize the breathlessness and to rank the top three. The investigators also have previous experience using these descriptors in the study of morphine for breathlessness (unpublished data).

Time points

Starting 2 days before concentrator delivery (Day 0), participants will complete a diary daily on Days -2 to 6. QOL will be measured on Days -2, 0 and 6, as per the Study Diagram presented in Figure 2.

Assessments and assessment burden

In an effort to minimize participant burden, the case report forms have been designed to be completed by the Clinical Research Nurse through objective observation and participant interviews. The patient diaries have been intentionally kept short to minimize burden.

Data Management & Analysis

- Clearly describe the data management plan
  - What is the error checking plan?
  - How will data discrepancies be resolved?
- Prepare an analysis plan linked to the specific aims
  - ***Work with a biostatistician!***
  - What tests will be used? What software?
  - What is the proposed frequency of analyses?
  - Are there any planned subgroup analyses?
  - How will missing data be handled?

– SAMPLE SIZE: What is the proposed sample size and what is the justification for the assumptions underlying the power calculations?

– ATTRITION: What is the likely rate of loss to follow up? On what evidence is the loss to follow-up rate based?

This section convinces the grant reviewers you
have a plan to finish the work and
it will produce meaningful results

Data Management (part of the section)

All study practices are detailed in the data management standard operating procedures (see Appendix B). Each site receives a specially prepared notebook detailing all of the data management procedures. The notebook also facilitates good record keeping practices.

Study data will be recorded in a number of files for both the administration of the study and collection of participant data. A master index will contain confidential patient contact information and will be the only link between individual patients and the PIN. This will be an Excel spreadsheet (Master patient index.xls) only accessible by password held by the PI, site investigators and data managers. There are no other records that can link individuals and their data. The Forms Tracking index will be identified by PIN only. It will be used to track the data forms for each participant for auditing of data collection. It will contain dates of when each form is due, entered and finalized (Forms tracking index.xls). The data file will be held and administered in the coordinating site, and will contain all the participant data as downloaded from the web site data forms. These data will then be transferred to the data set for analysis.

Analysis plan (part of the section)

For Specific Aim 1, the study objective will be addressed using a Mixed Model Repeated Measures (MMRM) analysis on the NRS dyspnea scores between randomization and day 6.105 The primary outcome is the breathlessness NRS, evening worst score. For Specific Aim 2, the study objective will be addressed using a MMRM analysis on the QOL scores between randomization and day 6. The main variable for this analysis is the global QOL score from the McGill. The MMRM approach offers superior control of Type 1 and Type 2 errors compared to the Last Observation Carried Forward approach.

Tests for statistical significance will be conducted using a 95% confidence interval for the treatment by time interaction. All comparisons will be made using intention-to-treat treatment groups defined at randomization.

Modeling of time will be treated using categorical variables rather than assuming a linear or quadratic relationship. Response variables are post-baseline values of measurements. Covariates are treatment, time, time by treatment, baseline measurements, and interactions of baseline measurements by time. To account for site-to-site differences in administrative procedures and patient populations, we will add indicators for site as random effects. Contrasts (along with 95% confidence intervals) of treatment by time will be used to estimate the difference in mean treatment change.

A secondary analysis of the dyspnea and QOL scores will be conducted by estimating treatment differences using a survival average causal effect approach (SACE).107 The SACE is a valid estimate of treatment effects among the subset of patient who would have survived to Day 6 on both treatments.

Sample Size Calculation

The sample size of 240 participants is based on the primary outcome variable and our experience in a crossover trial evaluating morphine and placebo for the treatment of breathlessness. NRS variance was estimated as 6, a 1 point change on the NRS was identified as a clinically relevant improvement, and 20% attrition rates were expected. We estimate that with 240 participants in this oxygen versus air randomized controlled trial we will have 80% power to detect a 1 point difference in the NRS with an α of 0.05. Data from the initial 40 patients suggests have our initial power calculations may have been slightly conservative as the estimated variance of the baseline NRS was 5.2. A 1 point change on the NRS is equivalent to a 10mm change on the VAS.

Ethical Considerations

- Demonstrate your understanding of the ethical concerns
  - Address the ethics of conducting research in people with advanced life-limiting illness
  - Describe any safety risks to participants
  - Is the study approved by the Ethics Committee or Internal Review Board?
  - Will there be a Data Safety Monitoring Board? What will be the makeup?
  - How will you protect participant confidentiality?
  - How will you deal with adverse events?

Pilot Testing

- Review all elements of the study that have been pilot tested
  - May be repeated from the preliminary studies
  - Demonstrate that the study is feasible
  - Demonstrate what you learned from the pilot study
    - How was the protocol modified?
    - Did the pilot provide background data for sample size calculations?

Evidence of pilot testing will provide critical proof of your commitment and capabilities

Other Items to Include

- Study timeline

Table 5: Study Timeline

MONTHS	1	2	3-6	7	8-21	22	23-24
Tasks	X	X					
Investigator preparations	X	X					
IRB amendments	X	X					
Clinical trial set up	X	X					
Hiring personnel	X	X					
Personnel training		X	X				
Participant recruitment			X	X	X		
Interventions			X	X	X		
Baseline data collection			X	X	X		
Follow up data collection			X	X	X		
Data entry			X	X	X		
Data cleaning				X	X	X	
Preparation of analysis code					X	X	
Analysis						X	X
Manuscript preparation	X	X	X	X	X	X	X
Debriefing & team support	X	X	X	X	X	X	X

- Study management plan
- Budget justification
- Resources pages
- Results dissemination plan
- Trial registration

Specifically Address the Challenges of Palliative Care Research

- Infrastructure
- Recruitment
- Palliative care setting
- Intervention modifications
- Attrition
- Ethical concerns
- Participant burden
- Missing data

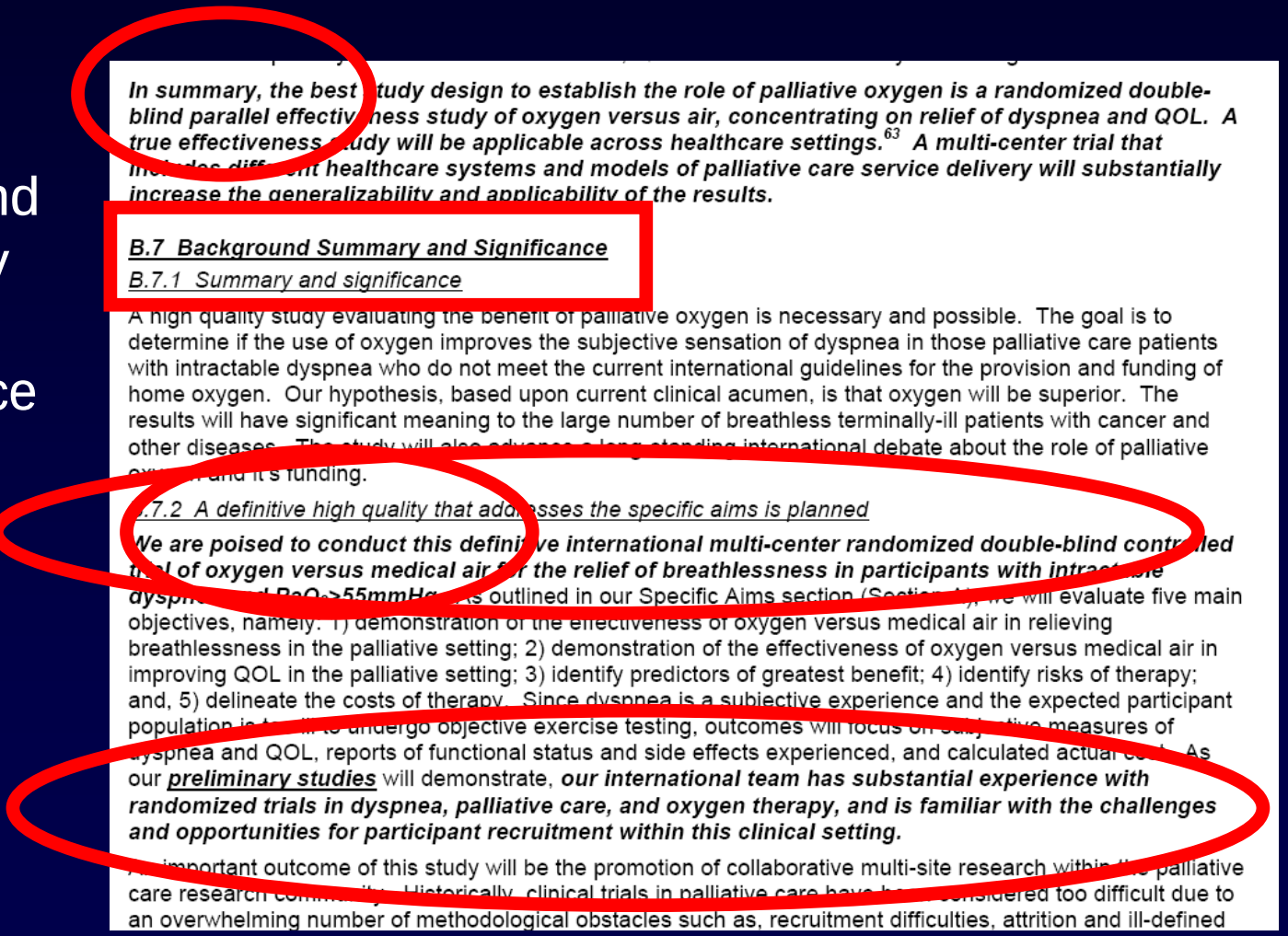
Other Useful Ideas

- Standard language
  - Resources pages
  - Data management
  - Ethics
- Handy buzz words
  - Critical, key, feature
  - Poised to conduct
  - High quality
  - Methodologically rigorous
- Use of bolding, bulleting, spacing, and fonts
  - Topic sentences
  - Main points
  - Summary statements

Direct Your Reader

Bo[illegible]ding, spacing

Background summary and significance



In summary, the best study design to establish the role of palliative oxygen is a randomized double-blind parallel effectiveness study of oxygen versus air, concentrating on relief of dyspnea and QOL. A true effectiveness study will be applicable across healthcare settings.[63] A multi-center trial that includes different healthcare systems and models of palliative care service delivery will substantially increase the generalizability and applicability of the results.

B.7 Background Summary and Significance

B.7.1 Summary and significance

A high quality study evaluating the benefit of palliative oxygen is necessary and possible. The goal is to determine if the use of oxygen improves the subjective sensation of dyspnea in those palliative care patients with intractable dyspnea who do not meet the current international guidelines for the provision and funding of home oxygen. Our hypothesis, based upon current clinical acumen, is that oxygen will be superior. The results will have significant meaning to the large number of breathless terminally-ill patients with cancer and other diseases. The study will also advance a long-standing international debate about the role of palliative [illegible] and it's funding.

B.7.2 A definitive high quality that addresses the specific aims is planned

We are poised to conduct this definitive international multi-center randomized double-blind controlled trial of oxygen versus medical air for the relief of breathlessness in participants with intractable dyspnea and PaO_2>55mmHg. As outlined in our Specific Aims section (Section [illegible]), we will evaluate five main objectives, namely: 1) demonstration of the effectiveness of oxygen versus medical air in relieving breathlessness in the palliative setting; 2) demonstration of the effectiveness of oxygen versus medical air in improving QOL in the palliative setting; 3) identify predictors of greatest benefit; 4) identify risks of therapy; and, 5) delineate the costs of therapy. Since dyspnea is a subjective experience and the expected participant population is [illegible] to undergo objective exercise testing, outcomes will focus on subjective measures of dyspnea and QOL, reports of functional status and side effects experienced, and calculated actual cost. As our ***preliminary studies*** will demonstrate, ***our international team has substantial experience with randomized trials in dyspnea, palliative care, and oxygen therapy, and is familiar with the challenges and opportunities for participant recruitment within this clinical setting.***

An important outcome of this study will be the promotion of collaborative multi-site research within the palliative care research community. Historically, clinical trials in palliative care have been considered too difficult due to an overwhelming number of methodological obstacles such as, recruitment difficulties, attrition and ill-defined

Other Useful Ideas

- Limitations section
- Don’t over-promise
- Volunteer to review proposals
- PROOFREAD YOUR GRANT
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    - PROOFREAD YOUR GRANT
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        - PROOFREAD YOUR GRANT
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ARE YOU READY?