

**Methodological Issues related to  
the use of Surrogate endpoints  
and Composite Outcome  
Measures in Critical Care Trials**

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# Study Team

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and Ulster Hospital

# Objectives

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- **Background and rationale**
- **Definitions and examples**
- **Research questions**
- **Proposed research**
- **Current status**
- **Aim for presenting at UKCCRF 2015**

# Background and Rationale

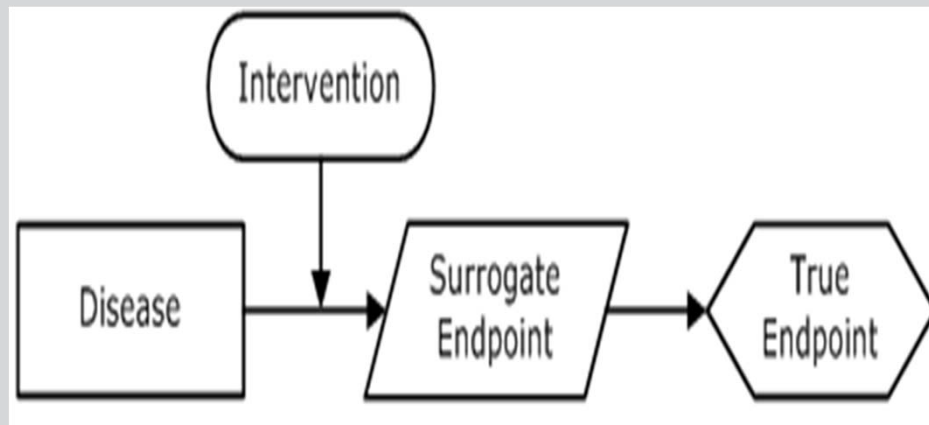
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- **Clinical trials are important for informing healthcare research**
- **Clinical end points takes long time to appear**
- **Use of Intermediate outcomes, biological markers, surrogate measures**
- **Simpler, faster and cheaper trials**

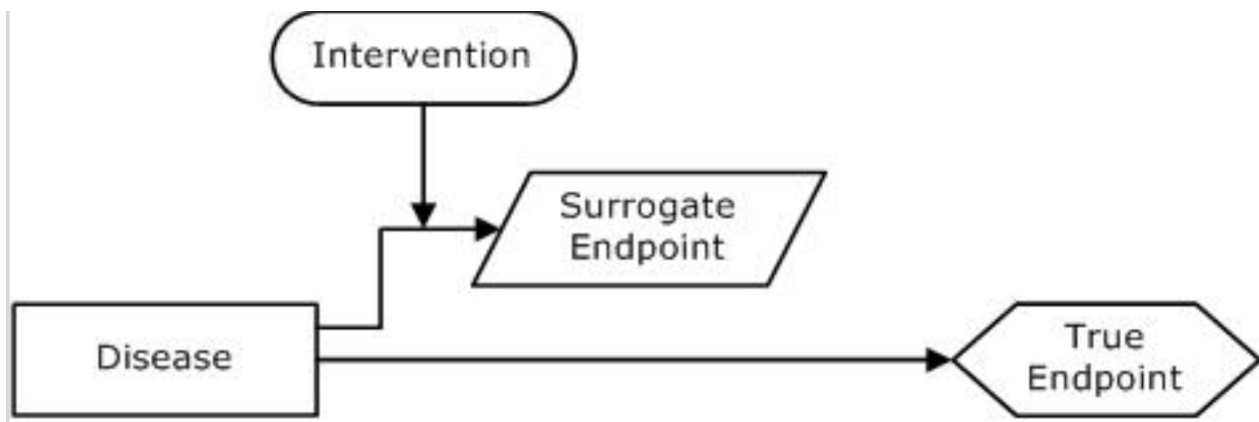
# What is a Surrogate Measure?

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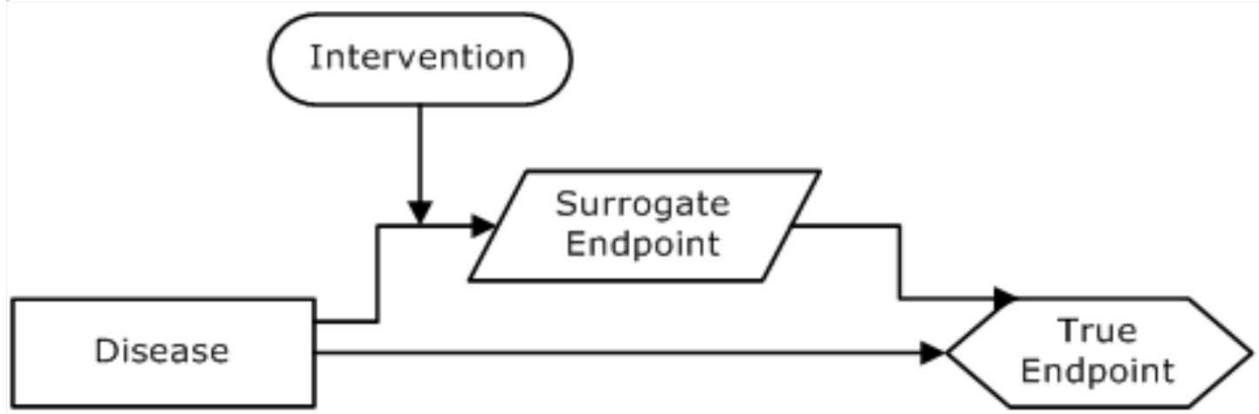
- A biomarker intended to substitute for a clinical endpoint. A clinical investigator uses epidemiologic, therapeutic, pathophysiologic, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm (National Institutes of Health working group)



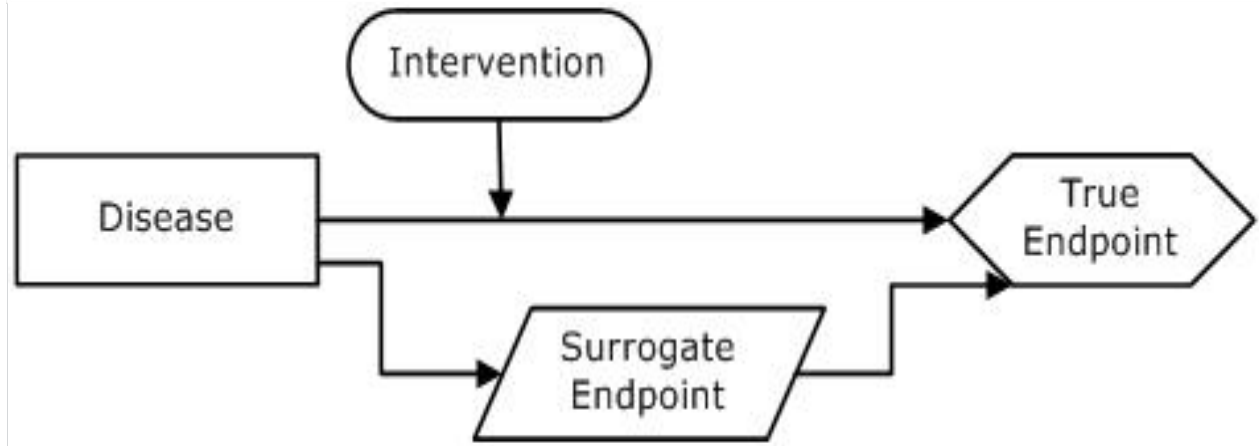
Gupta K et al., J Clin Res Best Pract, 2010, 8, 1-6



**Surrogate not  
in Causal  
Pathway**



**Surrogate not  
in all  
pathways**



**Surrogate not in  
the pathway of  
intervention effect**

# **Surrogate Measure in Mechanically Ventilated Patients**

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- **No valid surrogate outcome measures for Mechanically ventilated patients**
- **Can a surrogate or a set of surrogate measure provide a complete evaluation of long term patient status?**

# What is a composite measure?

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- **A composite outcome consists of two or more component outcomes.**
  - Eg. Ventilator free days (VFDs). VFDs combine mortality and duration of ventilation of survivors and are defined as the number of days alive and free from ventilation between successful weaning and day 28 after study enrolment.



# Composite Outcome in Critical Care Trials

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- **Limitations of use of Composite Outcome Measures**
- **Equal weighting for Death & 28 day ventilation**

# Background and Rationale

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- **No valid surrogate outcome measures for mechanically ventilated patients**
- **A surrogate or a set of surrogate measures provide a complete evaluation of long term patient status**

# Research questions

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- 1. What outcomes are used in early phase trials in Mechanically ventilated patients and how are they measured?**
- 2. What surrogate outcomes used in early phase trials can successfully predict patient-relevant outcomes in phase II trials?**
- 3. How useful is ventilator free days as an outcome and can its utility be enhanced by adjusting the ranking of death and duration of ventilation differently?**

# The Proposed Research

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- **Develop a Core Outcome Set (COS) for Early phase trials in Mechanically Ventilated Patients**
- **Evaluate the statistical methodologies used in the analysis of composite outcome measures and explore the option to develop a new statistical methodology**

# **STUDY 1. Develop a Core Outcome Set**

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- **Systematic review of outcome measures used in trials in MV patients**
- **Generate list of outcome variables**
- **Conduct statistical analysis to determine valid predictors**
- **Consensus meeting to agree COS**

# **STUDY 2. Analysis of Composite Outcome Measures**

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- **Systematic review of statistical methodologies to analyse composite outcome measures**
- **Evaluation of the methods identified, using HARP2 data and other trial data**
- **Identify the effects of scoring death different to 28 day ventilation**

# Current status

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- **Development of COS for early phase trials on mechanically ventilated patients is registered in COMET**

<http://www.comet-initiative.org/studies/details/709?result=true>

- **PROSPERO registration for systematic review 1 is in progress**

# Aim of presentation at UKCCRF

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- **Collaborators with relevant data**
- **General review and further research idea**



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Suggestions  
Questions  
Problems



25 – 26 June 2015

UK Critical Care Research Forum

Manchester Conference Centre