Introduction to Interrupted Time Series

Part I. Concepts

Joint CAPS/TAPS Methodology Seminar

January 19, 2016

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Main Goals

- Brief(ish) introduction to interrupted time series (ITS) designs
- Comparing ITS to some other quasi-experimental designs that do not include control groups.

Outline

- First look at an Interrupted Time Series (ITS)
- Gold standard: The randomized controlled trial design
- Generic threats to internal validity: RCTs
- Some quasi-experimental designs (QED) with no control group
- Generic threats to internal validity: QEDs
- The ITS design; real examples of some archetypal outcomes
- Bolstering the ITS design
- ITS analysis, very briefly
- Summary

First look at an Interrupted Time Series Design

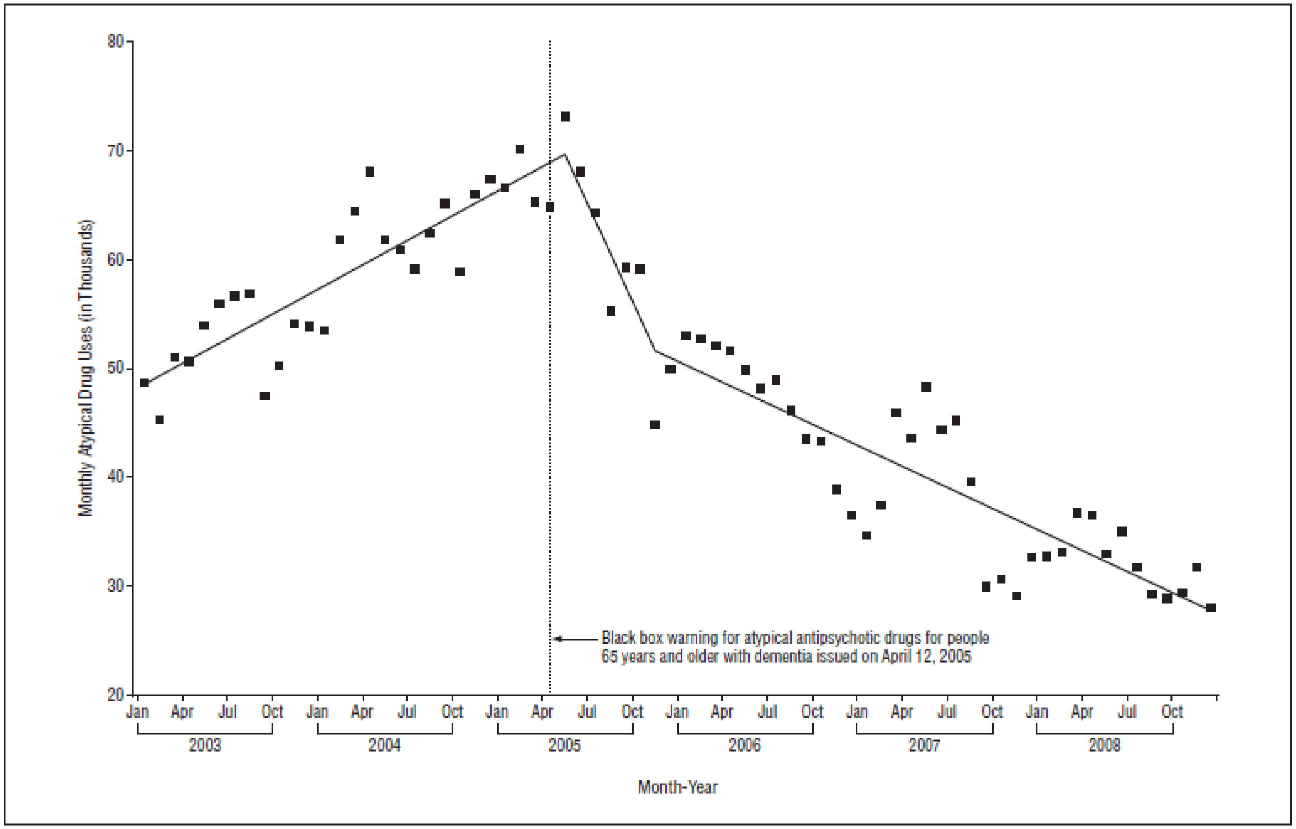


Figure 2. Joinpoint Regression Program analysis for atypical antipsychotics use among elderly patients with dementia. The data points represent patients 65 years and older with dementia (smoothed 6-month averages); the solid line, fitted joinpoint time series.

2010. Dorsey, RE et al. *Arch Intern Med*, 170, 96–103

April 2005: FDA issued an advisory and black box warning

Risks of ↑ mortality: atypical anti-psychotic use: elderly patients w/ dementia

The impact of these warnings on atypical drug use was unknown

Gold Standard: The Randomized Controlled Trial Design

$$\text{Rnd} \begin{cases} \text{Intv:} & O_{t1} & \mathbf{Tx} & O_{t2} \\ \text{Ctrl:} & O_{t1} & & O_{t2} \end{cases}$$

- Rnd: Equivalent groups at t_1.

- If 'closed-system' maintained,
  then solid basis for causal inference about Tx effects

I.e., internal validity

Generic Threats to Internal Validity

Focal (for today)

- **Selection**: participant characteristics systematically differ across groups
- **History**: events acting upon population & co-occurring with Tx
- **Maturation**: natural changes in sampled Pts across time
- **Testing**: repeated exposure to a test may affect assessment

Generic Threats to Internal Validity

Others—almost universally problematic

- **Instrumentation**: the nature of a measure changes across time, such that the validity of repeated assessments may be questioned

- **Ambiguous temporal sequencing of variables**: $X \rightarrow Y$, or $Y \rightarrow X$?

- **Regression**: Pts with initial extreme values may 'regress'

- **Attrition**: if systematically correlated with Tx or outcomes

All threats (Focal and Others) can combine additively or interactively

RCT and 'Focal' Threats to Internal Validity

$$\text{Rnd}\begin{cases}\text{Intv:} & O_{t1} & \textbf{Tx} & O_{t2} \\ \text{Ctrl:} & O_{t1} & & O_{t2}\end{cases}$$

Selection: randomization should address

History: synchronized assessments should address

Maturation: randomization & synchronized assessments should address

Testing: parallel assessment schedule should address

RCT and 'Other' Threats to Internal Validity

$$\text{Rnd}\begin{cases}\text{Intv:} & O_{t1} & \mathbf{Tx} & O_{t2} \\ \text{Ctrl:} & O_{t1} & & O_{t2}\end{cases}$$

Instrumentation: addressed, as long as measures are relevant to targeted constructs

Ambiguous temporal sequencing: longitudinal design addresses

Regression: randomization and parallel assessments should address, even if extreme groups are targeted for recruitment

Attrition: always a concern; to be dealt with in a principled fashion

Some Longitudinal QED designs w/ no Control Group

Often, QI study designs do not employ a control group

	One Sample, Longitudinal	Multiple-Cross Sections
pretest-posttest	O_{t1} **Tx** O_{t2}	O_{t1} **Tx** O_{t2}
pre-post w/ multi-pre	O_{t0} O_{t1} **Tx** O_{t2}	O_{t0} O_{t1} **Tx** O_{t2}
repeated Tx	O_{t1} **Tx** O_{t2} ~~**Tx**~~ O_{t3} **Tx** O_{t4}	O_{t1} **Tx** O_{t2} ~~**Tx**~~ O_{t3} **Tx** O_{t4}

- Many other designs exist

Summary: Internal Validity Threats w/ no Control Group

One-Sample, Longitudinal QEDs

	selection	history	maturation	testing
O_{t1} Tx O_{t2}		x	x	x
O_{t0} O_{t1} Tx O_{t2}		x	reduced	x
O_{t1} Tx O_{t2} ~~Tx~~ O_{t3} Tx O_{t4}		greatly reduced		x

Multiple-Cross Sectional, QEDs

	selection	history	maturation	testing
O_{t1} **Tx** O_{t2}	x	x	x	
O_{t0} O_{t1} **Tx** O_{t2}	x	x	reduced	
O_{t1} **Tx** O_{t2} ~~**Tx**~~ O_{t3} **Tx** O_{t4}	x	reduced		

The Interrupted Time Series Design

- Longitudinal

O_{t1} O_{t2} O_{t3} O_{t4} O_{t5} **Tx** O_{t6} O_{t7} O_{t8} O_{t9} O_{t10}

- Multiple cross-section

O_{t1} O_{t2} O_{t3} O_{t4} O_{t5} **Tx** O_{t6} O_{t7} O_{t8} O_{t9} O_{t10}

Either way, it can be a strong design

ITS Example 1: Charging for directory assistance (DA)

- A change in level at intervention onset (March 1974). Y-axis: # calls

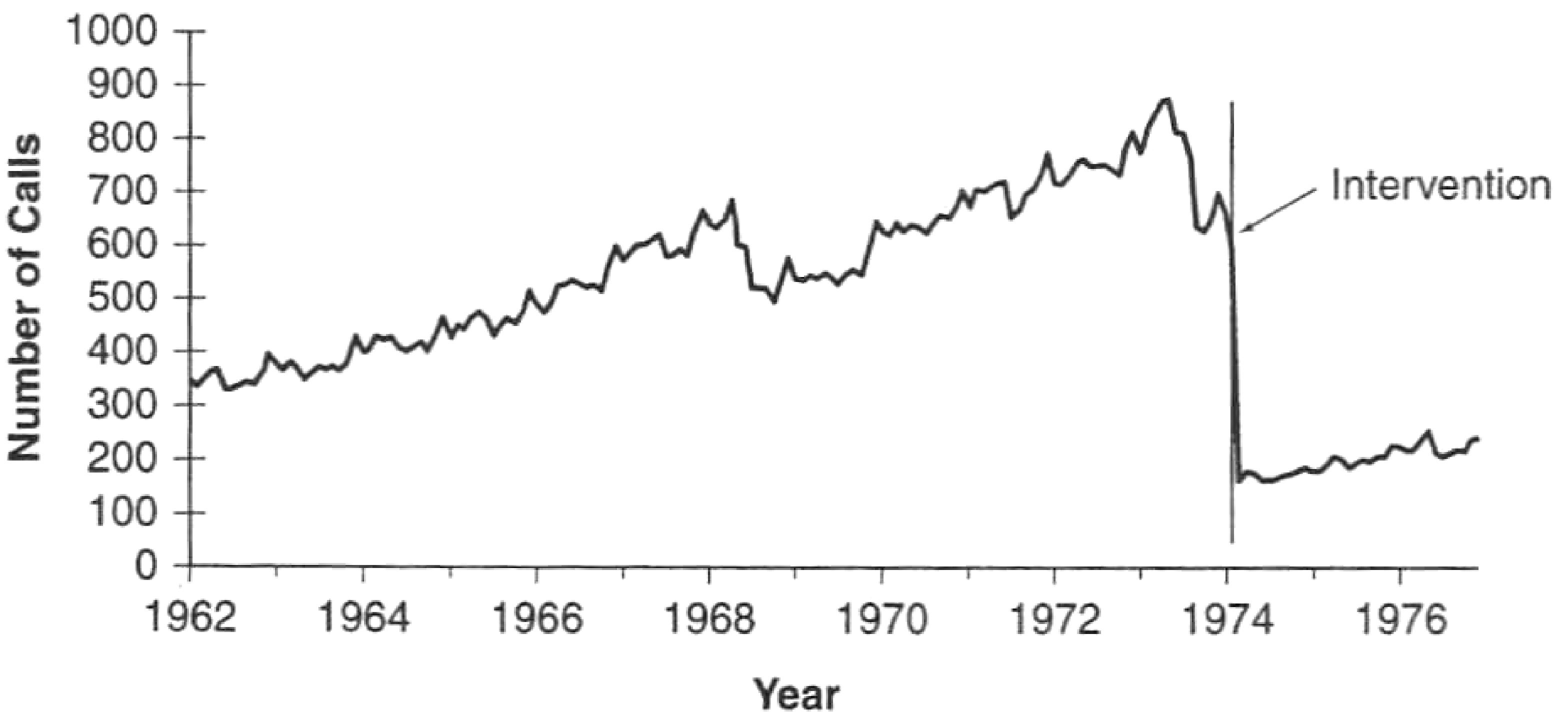


FIGURE 6.1 The effects of charging for directory assistance in Cincinnatii

ITS Example 1: Charging for directory assistance (DA)

- Immediate large drop in number of calls, March 1974

Selection implausible:
pre and post samples likely the same

Attrition implausible
New charges unlikely to prompt phone disconnections

Maturation implausible
no known maturation process could account for drop in calls

History implausible
unless another hypothetically causal event can be identified

Testing implausible
E.g., if phone co. changed salience of DA charges on phone bills

Regression to the mean implausible:
pre- trend suggested high call rates for many years

ITS Example 2: New Law Re. Sexual Assault Reporting

- Change in slope at intervention onset. Y-axis: # reported sexual assaults

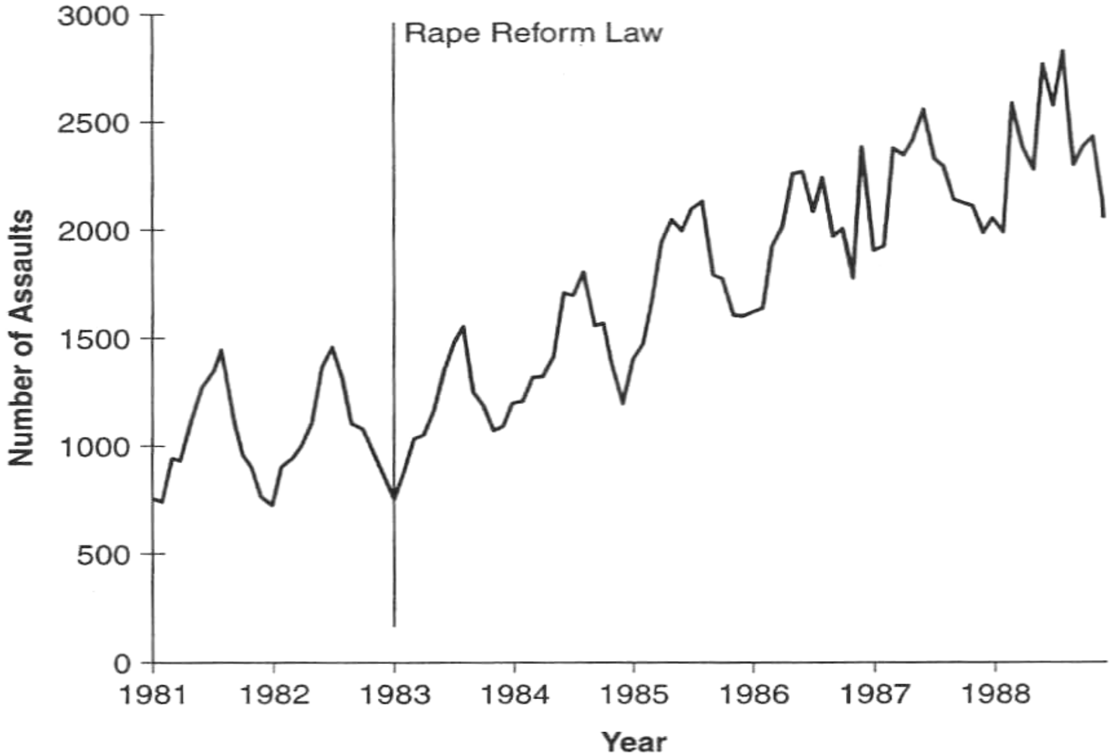


FIGURE 6.2 The effects of sexual assault law reform in Canada

From "Reforming rape laws: Effects of legislative change in Canada," by J. V. Roberts and R. J. Gebotys, 1992, *Law and Human Behavior, 16*, 555–573. Copyright 1992 by Kluwer Academic/Plenum Publishers.

Canada 1983 included highly publicized provisions to increase reporting to police

Note seasonal variation

ITS Example 2: New Law Re. Sexual Assault Reporting

- Immediate change in slope from flat to positive, 1983

Maturation implausible
no known maturation process could account for change in slope

History implausible
unless another hypothetically causal event can be identified

Instrumentation possible.
The new law changed the categories of reportable sexual assault
1. wives could charge husbands with sexual assault
2. included assaults against both males and females

Authors showed that, in the post-intervention period,
suspects who were women or husbands
did not increase sufficiently to explain the pattern of results.

ITS Example 3: Alcohol warning label re. prenatal drinking

- Weak, Delayed, Ambiguous Effects. Y-axis: Prenatal Drinking Score

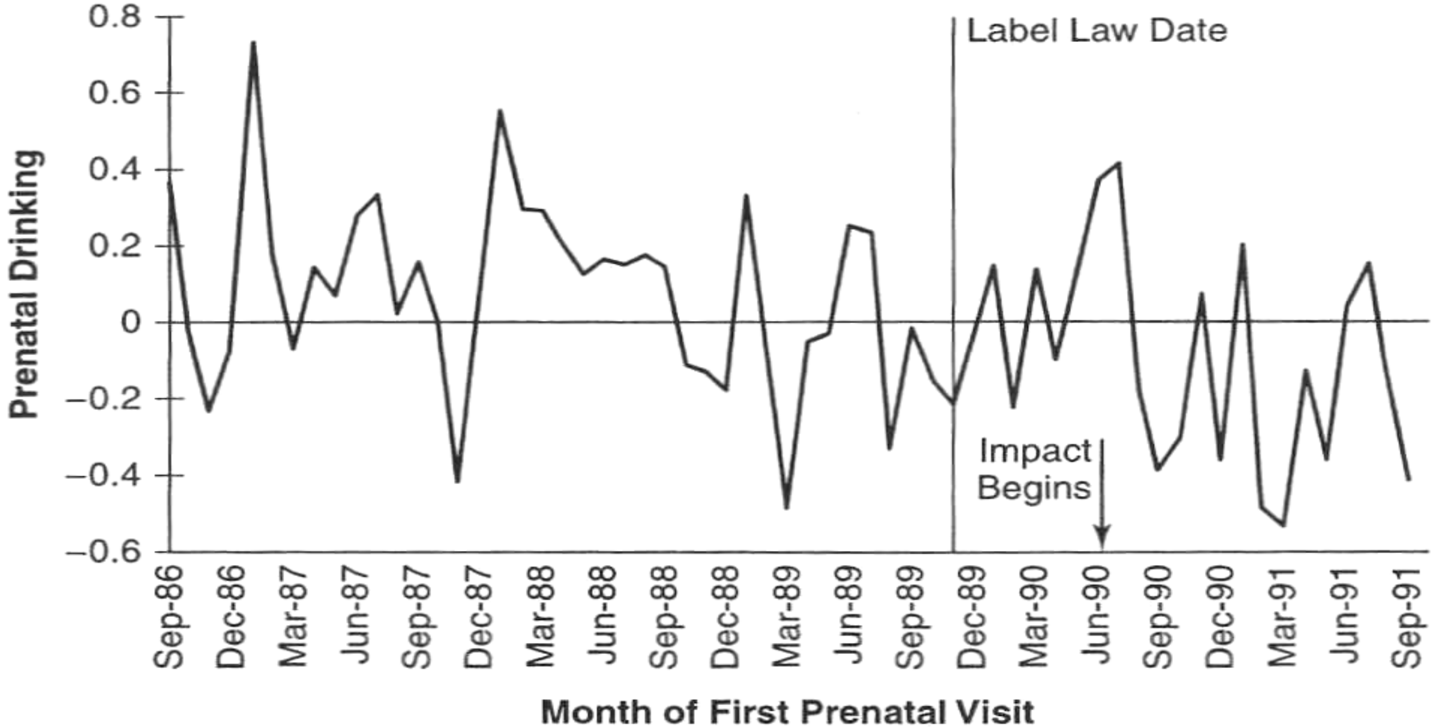


FIGURE 6.3 The effects of an alcohol warning label on prenatal drinking

From "A time series analysis of the impact of the alcohol warning label on antenatal drinking," by J. R. Hankin et al., 1993, *Alcoholism: Clinical and Experimental Research, 17,* pp. 284–289. Copyright 1993 by Lippincott, Williams &

DV: Alcohol consumption 2 weeks prior to 1st prenatal visit

ITS Example 3: Alcohol warning label re. prenatal drinking

Delayed effect, authors argued, 7 months after implementation

- Law affected new containers, not those already on store shelves
- When asked, women were not aware of the labels until +4 months

Maturation threat? Drinking was decreasing prior to the intervention

- Analysis: *delayed* Tx slope was stronger than pre-Tx slope

Seasonal variation threat?

- Typically, drinking increased during Nov/Dec and Summer
- Given intervention timing & results, seasonality not a strong threat
- November onset: Seasonal & treatment effects in opposite directions
- If intervention implemented in Feb or Sept, then seasonal effects might be misinterpreted as intervention effects.
- Much lower rates in Nov/Dec ‘90 and Summer ‘91
  - Compared to holiday/summer periods in previous years

ITS Example 4: Pay-for-performance & BP control

- No effect observed

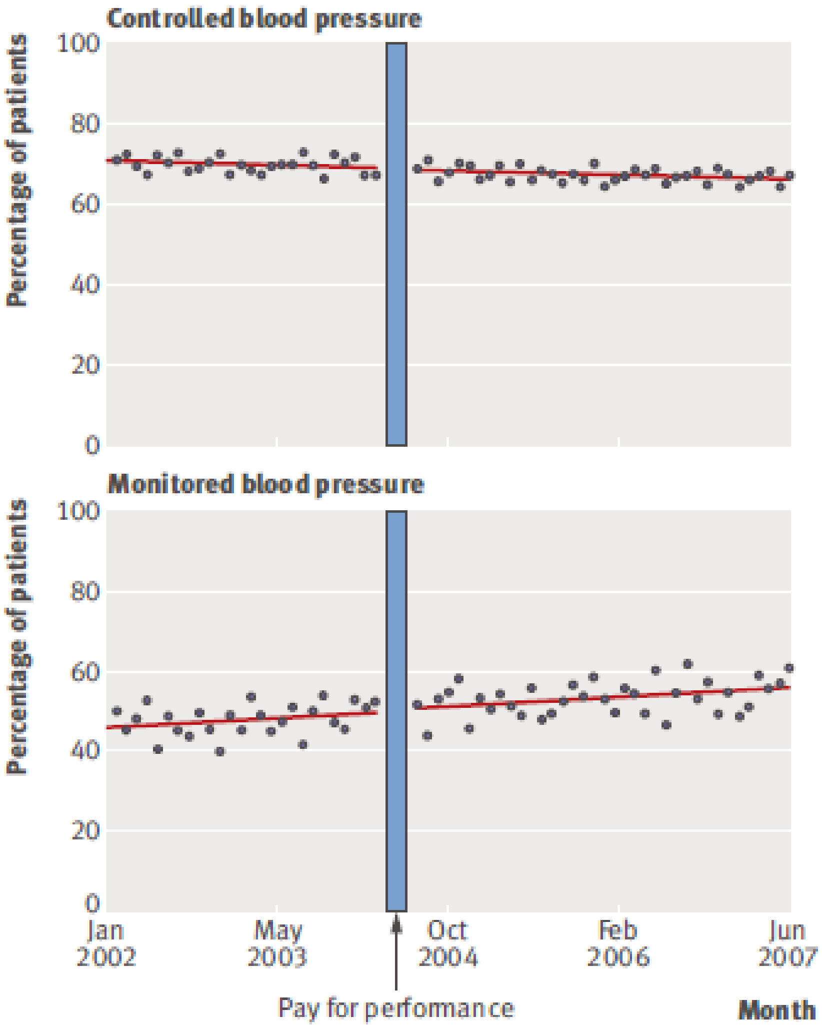


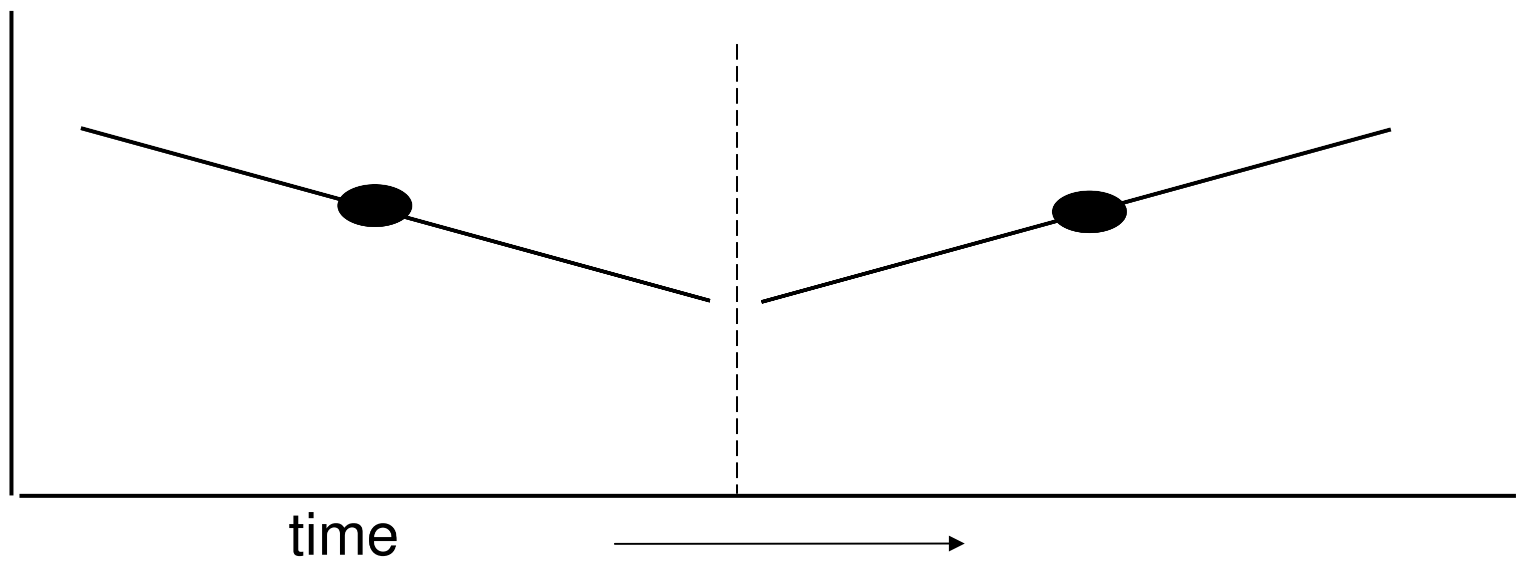
Fig 2 | Effect of pay for performance on blood pressure control and monitoring in United Kingdom

ITS advantages over pre-test / post-test design: Simplified

Scenario #1: intervention effect observed: immediate change in slope

. ITS would identify the intervention effect

. A simple pre-post test design would not.
Comparing the pre- and post- means (black dots) suggests no overall pre-post difference

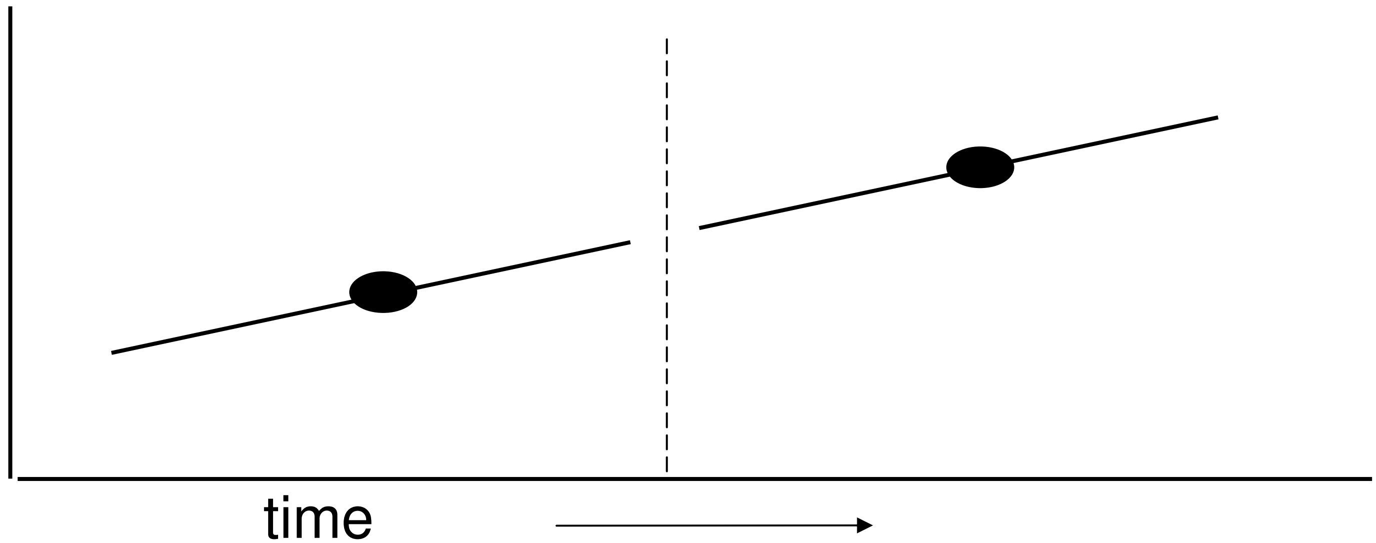


ITS advantages over pre-test / post-test design: Simplified

Scenario #2: no intervention effect

. ITS would identify the lack of intervention effect

. A simple pre-post test design would suggest an intervention effect.
Comparing pre- and post- means (black dots) suggests
a post-test increase in outcome level



Summary, So Far

- ITS design can provide a good basis for drawing causal inferences if…

  . observed changes are well timed with intervention onset

  . alternative explanations (threats to internal validity) are *implausible*

- However, even under those circumstances
  threats to internal validity may still operate,
  e.g., the seemingly implausible may obtain

- Next: ways to bolster the ITS design

Bolstering the ITS Design

- Non-equivalent no-treatment control group
- Non-equivalent dependent variables
- Removing a treatment at a known time
- Multiple replications
- Switching replications

Bolstering the ITS Design

Non-equivalent, no-treatment control group

O_{t1} O_{t2} O_{t3} O_{t4} O_{t5} **Tx** O_{t6} O_{t7} O_{t8} O_{t9} O_{t10}

O_{t1} O_{t2} O_{t3} O_{t4} O_{t5} **Tx** O_{t6} O_{t7} O_{t8} O_{t9} O_{t10}

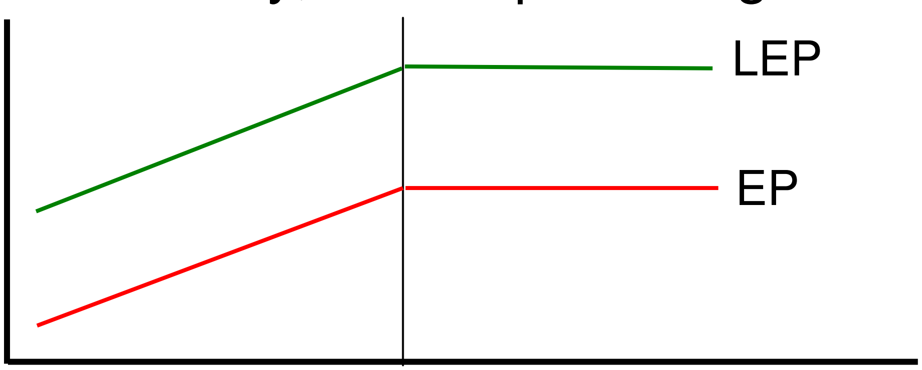
<u>Concept</u>

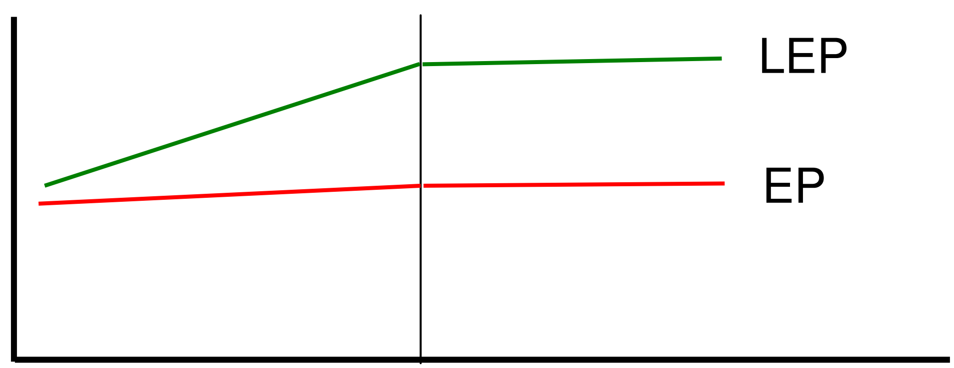
- I.e., add a group hypothetically unaffected by the intervention

<u>Example: L. Karliner (PI)</u>

Impact of hospital "bedside interpreter" on LEP patient outcomes
(add a non-equivalent no-treatment control group of EP patients)

Most notably, this helps to diagnose **history** threats (made-up examples)





Bolstering the ITS Design

Non-equivalent, no-treatment control group

Addressing threats to internal validity

History
EP & LEP patients live in same city, treated in same hospital
So, many potential historical effects would be equivalent

Instrumentation
If hospital charts and billing record systems changed,
then the change should affect both EP and LEP groups

Selection: here non-equivalence of groups is intentional
A problem could arise if history and selection effects interacted
to produce differential group effects around the time
of intervention onset

Bolstering ITS Design:

Non-equivalent dependent variables

$$\frac{O_{At1}\quad O_{At2}\quad O_{At3}\quad O_{At4}\quad O_{At5}\quad \mathbf{Tx}\quad O_{At6}\quad O_{At7}\quad O_{At8}\quad O_{At9}\quad O_{At10}}{O_{Bt1}\quad O_{Bt2}\quad O_{Bt3}\quad O_{Bt4}\quad O_{Bt5}\quad \mathbf{Tx}\quad O_{Bt6}\quad O_{Bt7}\quad O_{Bt8}\quad O_{Bt9}\quad O_{Bt10}}$$

Concepts

Add an outcome hypothesized to be unaffected by the intervention,

Main & non-equiv. DVs should be equally subject to validity threats

Main & non-equivalent DVs should be conceptually related

Example: Directory assistance (DA)

The DA charge was only for local numbers, not long distance (LD)

The author noted that only local DA calls changed, not LD DA calls

Bolstering ITS Design: British Breathalyzer example

Non-equivalent dependent variables

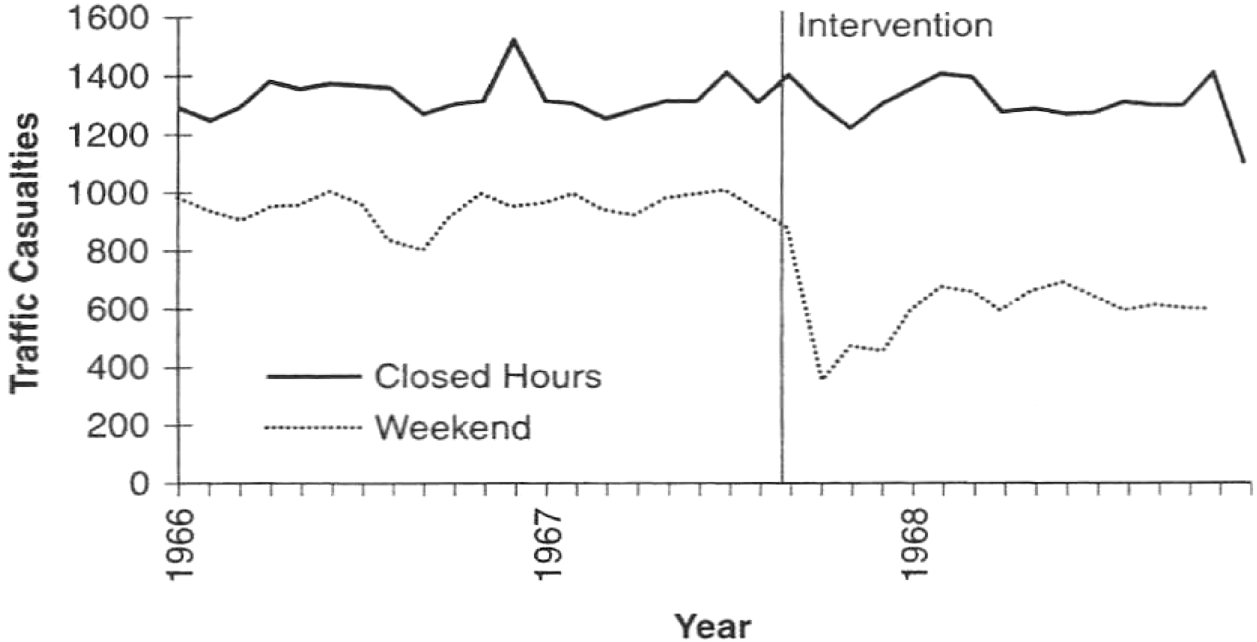


FIGURE 6.6 The effects of the British Breathalyzer crackdown on traffic casualties during weekend nights when pubs are open, compared with times when pubs were closed

From "Determining the social effects of a legal reform: The British 'breathalyser' crackdown of 1967," by H. L. Ross, D. T. Campbell, and G. V. Glass, 1970, *American Behavioral Scientist, 13,* pp. 493–509. Copyright 1970 by Sage

Closed hours: e.g., commute times

History threats (e.g., ↑ speed traps, safer cars)
should affect all serious accidents regardless of time of day

Bolstering the ITS Design

Removing a treatment at a known time

O_{t1} O_{t2} O_{t3} O_{t4} **Tx** O_{t5} O_{t6} O_{t7} ~~**Tx**~~ O_{t8} O_{t9} O_{t10}

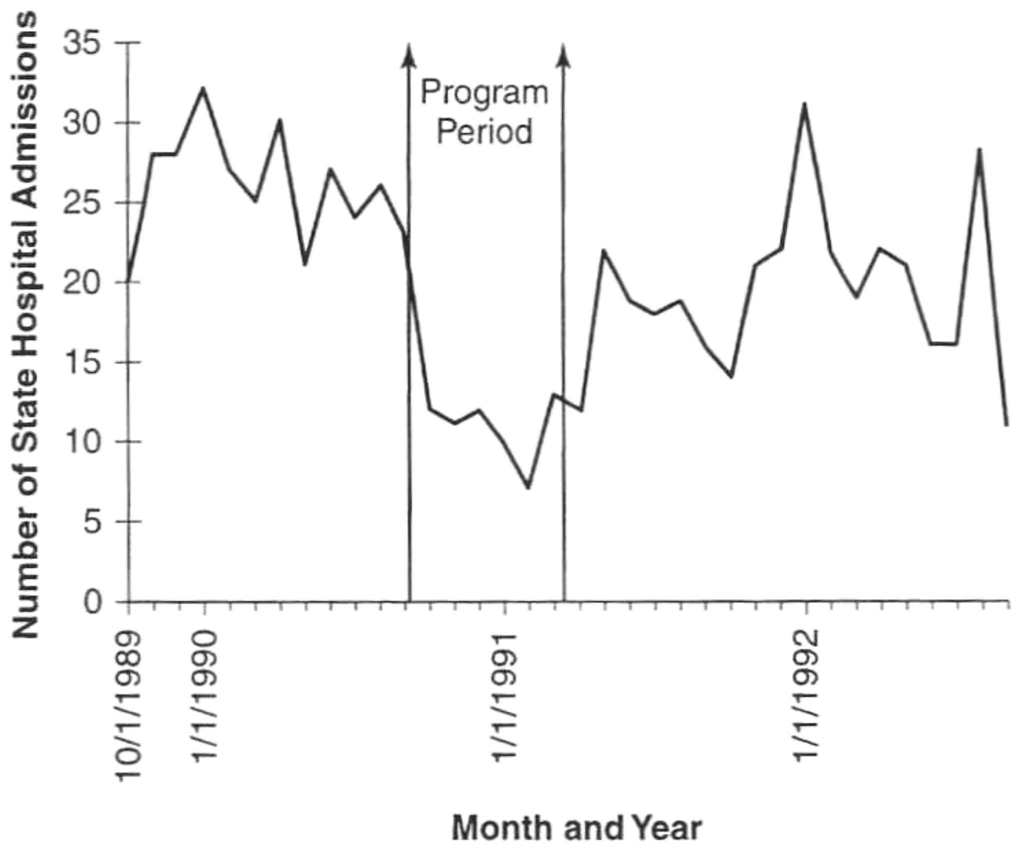


FIGURE 6.8 The effects of psychiatric crisis intervention on hospitalization

From "Around-the-clock mobile psychiatric crisis intervention: Another effective alternative to psychiatric hospitalization," by G. R. Reding and M. Raphelson, 1995, *Community Mental Health Journal, 31*, pp. 179–187.

Bolstering the ITS Design
Removing a treatment at a known time

Addressing threats to internal validity

History

If the hypothesized response pattern obtained, then
a credible historical threat would require one or more effects that
i. operate in different directions at different times, and
ii. are well-timed with intervention onset and removal

Selection

If this treat were credible, then it would require different types of people to enter and leave the population at different times

Instrumentation

A less plausible threat with this design

Non-equivalent control group would provide additional strength regarding possible History and Maturation (e.g., seasonal trend) effects

Bolstering the ITS Design

Adding multiple replications

O_{t1} O_{t2} **Tx** O_{t3} O_{t4} ~~**Tx**~~ O_{t5} O_{t6} **Tx** O_{t7} O_{t8} ~~**Tx**~~ O_{t9} O_{t10}

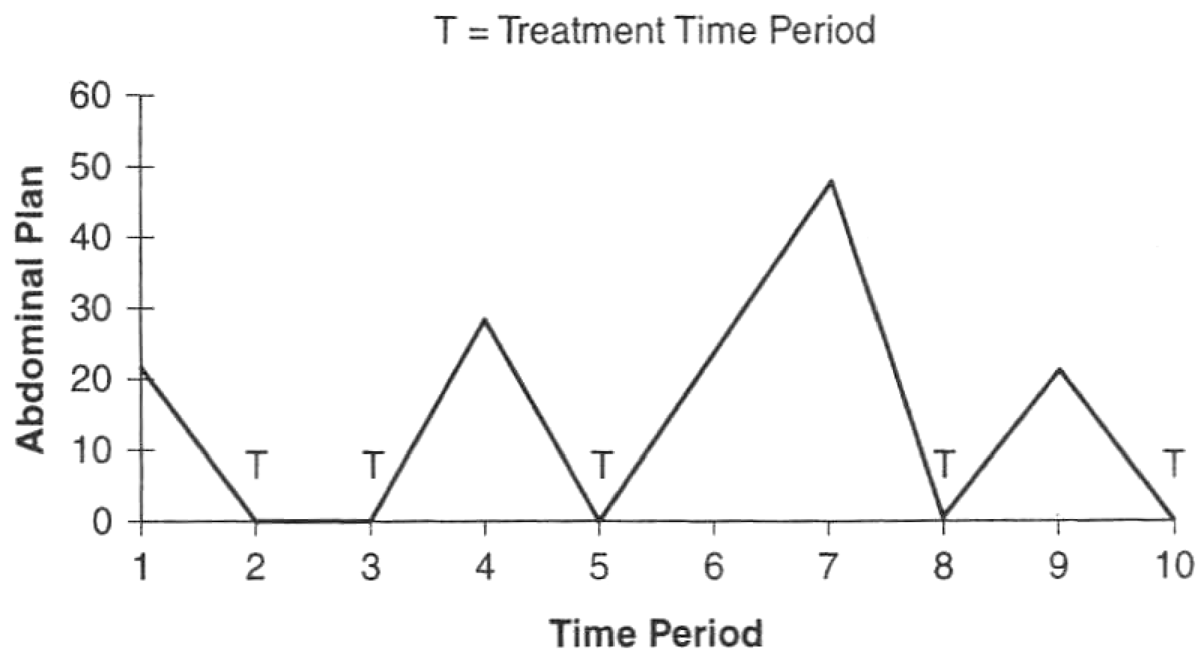


FIGURE 6.9 The effects of treatment for inflammation of continent ileostomy. In the graphs, the letter *T* indicates the time period during which treatment occurred

From "Single patient randomized clinical trial: Its use in determining optimal treatment for patient with inflammation of a Kock continent ileostomy reservoir," by R. S. McLeod et al., 1986, *Lancet, 1*, pp. 726–728.

Bolstering the ITS Design

Adding switching replications

2 or more nonequivalent groups w/ staggered intervention introduction

O_{t1}	O_{t2}	O_{t3}	**Tx**	O_{t4}	O_{t5}	O_{t6}	O_{t7}		O_{t8}	O_{t9}	O_{t10}
O_{t1}	O_{t2}	O_{t3}		O_{t4}	O_{t5}	O_{t6}	O_{t7}	**Tx**	O_{t8}	O_{t9}	O_{t10}

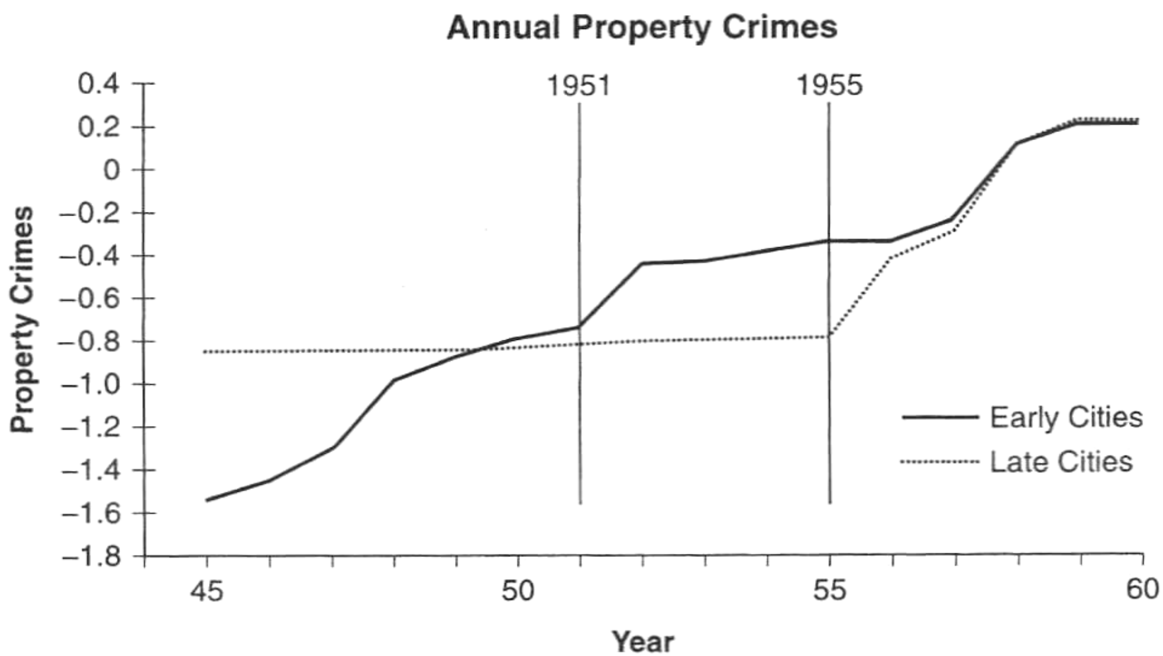


FIGURE 6.10 The effects of the introduction of television on property crime rates in cities in which television was introduced in 1951 versus 1955

From "The evolution of the time series experiment," by R. D. McCleary, 2000, *Research design: Donald Campbell's legacy, Vol. 2,* edited by L. Bickman, Thousand Oaks, CA: Sage. Copyright 2000 by Sage Publications.

Bolstering the ITS Design

Longitudinal cohort studies

Patient-level data, longitudinally collected before and after an intervention (e.g., surgery).

E.g., prospective cohort study where patients are followed for 10 years
- Some have a surgical intervention during the study observation period
- Interest is in comparing pre- and post-surgical outcome trends

Possible to model patient-level time series as switching replications
- However, individual patient time series may be very noisy and some patients will have very few pre- or post-surgery observations

An alternative is to code the time of each patient's surgery as time=0,
- pool data across patients, and
- model using repeated measures regression

Analysis of data from ITS designs

Originally, time-series analysis, a modeling framework from econometrics, was used almost exclusively

Analysis Alternatives

. Repeated measures models
. Segmented linear regression

We will discuss some analysis options during the 2nd hour

Summary

- ITS vs. other QED wrt threats to internal validity
  - . ITS far superior to pre-/post-test type designs with no control group
  - . ITS better than pre-post designs with an unmatched, non-randomized control group
  - . ITS can be better than pre-post designs with a matched non-randomized control group sample
- A suggested 'minimal' ITS design
  - . intervention onset at a single point in time
  - . intervention delivered to one population
  - . add a non-equivalent control group
  - . add non-equivalent outcomes, if possible
- Often attainable advanced design element: Switching replications
  - . A natural addition when working in multiple practices within a system, multiple hospital systems, etc.

Summary

- Units of analysis

    Outcomes often aggregated monthly, quarterly, or annual summaries

    e.g., annual incidence of a specific condition,

    total quarterly costs, average (or median)

- Trade-off between length of observation, level of aggregation, noise

- Signal-to-noise ratio

    Series of patient-level outcomes can be very noisy, even in aggregate

    This may require large numbers of observations

    May not be feasible for some studies with primary data collection

    Longitudinal (vs. multiple cross-sectional) data help wrt power

    Experience is the best guide

- Medical records, billing data, claims data, administrative data

    Opportunities to evaluate clinical policy changes, either

    . Truly retrospectively

    . Semi-prospectively, with the aid of retrospective pre- data

END