Cluster vs. Conventional RCT Design in Low Event Rates

Prevention of Arrhythmia Device Infection Trial (PADIT) Cluster Crossover Pilot Study

CANNeCTIN Biostatistics Methodology Videoconference

January 14, 2011

The David Braley Cardiac, Vascular &
Stroke Research Institute (DBCVSRI)
Hamilton, Ontario

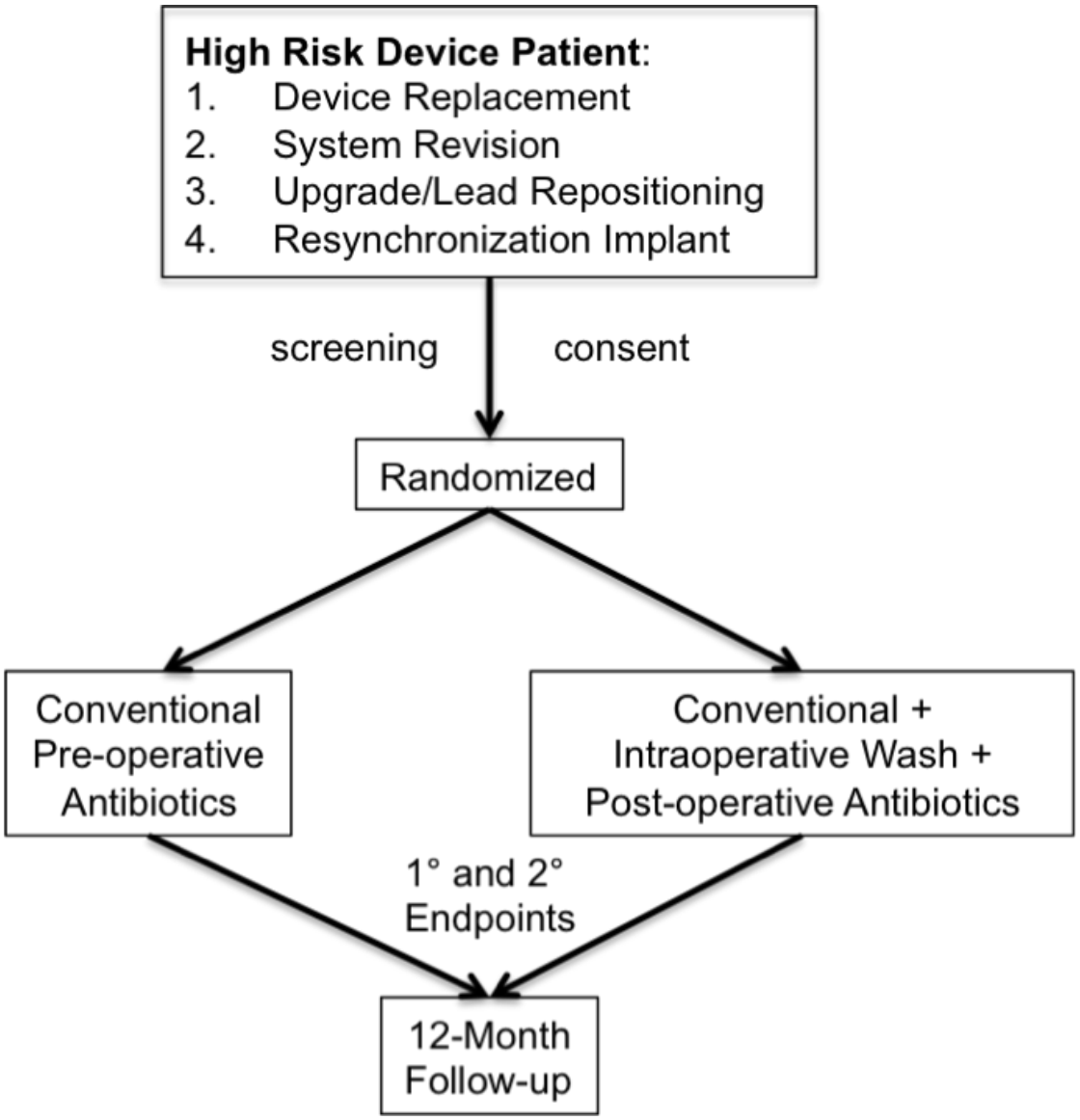
Outline

1. Brief review of the ‘classic ‘ design of PADIT and the feasibility issues that arise – number of patients and fee per patients.
2. Results of Pilot to date.
3. Introduce the concept of a cross-over design as a way to test a ‘systems’ approach to care.
    1. Explain how it makes it easier for sites by allowing them to treat all their patients the same way over extended periods
    2. Explain the consent process
    3. Review the ethical issues
    4. Review the sample size issues and how we used the ICES data to develop the estimates.

Background

- EP Community meets annually to think tank at CCC
- Plenty of “orphan” ideas that do not have industry support
- Strong history of collaborative research
  - CIDS, CTOPP, POST, CHRS DAC
- 2008 CCC meeting birthed 2 potential projects to bring forward to CANNeCTIN
- Device infection prevention study - 28,000/year 
  - Catastrophic outcome in 2% of patients
  - Case series but no comparative studies
  - Pilot funded by CANNeCTIN started Dec 2009

Prevention of Arrhythmia Device Trial (PADIT)



Study Progress

- Principle of simplicity
  - Large scale simplified to drive down complexity of consent, ethics process, administration and cost
- CIHR RCT Application Sept 2009
  - Score 2.87, rank 26/35, 3/35 grants funded
  - Major concerns:
    - Justification of lack of blinding, nature and duration of intervention, sparse follow-up
    - Lack of pilot data
    - Low budget of $100/patient

Overall Status

Total Number of Sites: **11**

Total Number Pts. Recruited: **500**

Timelines

First Patient In: **Dec 17, 2009**

Last Patient In: **Dec 8, 2010**

Last Follow Up Visit: **Dec 8, 2011**

Padit Pilot: Recruitment by Month
As of December 8, 2010

Month	Active Centres	Patients Randomized
December-2009	2	4
January-2010	3	16
February-2010	6	33
March-2010	8	55
April-2010	8	62
May-2010	9	46
June-2010	10	66
July-2010	10	56
August-2010	10	43
September-2010	10	37
October-2010	11	39
November-2010	11	37
December-2010	11	6
Total	11	500

Padit Pilot: Patient Randomization by Centre
As of December 8, 2010

				Patients Randomized the week of						
Centre Number	Centre	Doctor	Activity up to NOV 07, 2010	NOV 07, 2010	NOV 14, 2010	NOV 21, 2010	NOV 28, 2010	Total	Last 4 Weeks	Average Per Week
1	London Health Sciences Centre University Hospital	Dr. Andrew Krahn	107	1	3	0	1	112	5	2.5
2	St. Michael's Hospital Division of Cardiology	Dr. Iqwal Mangat	31	0	1	0	2	34	3	0.9
3	Ottawa Heart	Dr. Pablo Nery	17	0	0	0	0	17	0	0.6
4	Institut universitaire de cardiologie et de pneumologie de Québec	Dr. Francois Philippon	103	2	1	0	2	108	5	2.1
6	Southlake Regional Health Centre	Dr. Yaariv Khaykin	40	1	0	1	2	44	4	1.0
7	University of Calgary	Dr. Derek Exner	65	0	0	0	0	65	0	1.6
8	Queen Elizabeth II Health Sciences Centre	Dr. Ratika Parkash	27	0	2	2	0	31	4	1.0
11	MUHC, Montreal General Hospital	Dr. Vidal Essebag	36	0	0	0	0	36	0	1.2
12	McMaster University	Dr. Jeff Healey	27	0	0	0	0	27	0	0.6
13	St. Mary's General Hospital	Dr. Claus Rinne	17	0	0	1	1	19	2	0.7
14	Kingston General Hospital	Dr. Chris Simpson	3	1	0	0	2	6	3	1.0

Overview of PADIT Cluster Cross-Over

- Randomize pacemaker centres to 2 ‘systems’ of prophylactic antibiotics for prevention of device infection
- Centres will cross-over after a wash-out period
- All patients will receive the ‘system’ in use at the time
- Eligible patients will be asked for consent to use their data for the study
- Outcome is serious device infection within one year

Why a Cluster Design?

Hypothesis: Does one system of care improve outcomes compared to another system

- Cardiac rhythm devices are implanted in specialized centres
- These are very high volume centres of excellence
- Implant procedures are highly systematized and follow standard operating procedures
- Achieve uniformity of practice and adherence to best practice

- Randomizing the centres 'systems of care' will best test the hypothesis

Cross-Over Design

- Reduces variation between treatment arms
- Improves study power
- Risk of ‘contamination’ needs to be assessed and managed by a ‘wash-out’ period

Ethical Considerations

- Exquisite Clinical Equipoise between systems of care
- All patients at site receive the allocated treatment during the study periods
- Eligible patients asked for consent to use their data for the analysis
- In usual clinical practice, systems of care are routinely changed, without patient consent or notification

PADIT CX-O Pilot Study

- Funded by CANNeCTIN (Peer Reviewed)
- 6 centres
  - Includes 5 university and one community centre
- 2 month treatment periods
  - Or maximum of 40 patients per site
- Two centres have submitted to Ethics Committees

Conclusion

- Cluster Cross-over Trials may be useful technique to practically evaluate different systems of care
  - Clinical equipoise is clear
  - Cross-over without contamination is possible

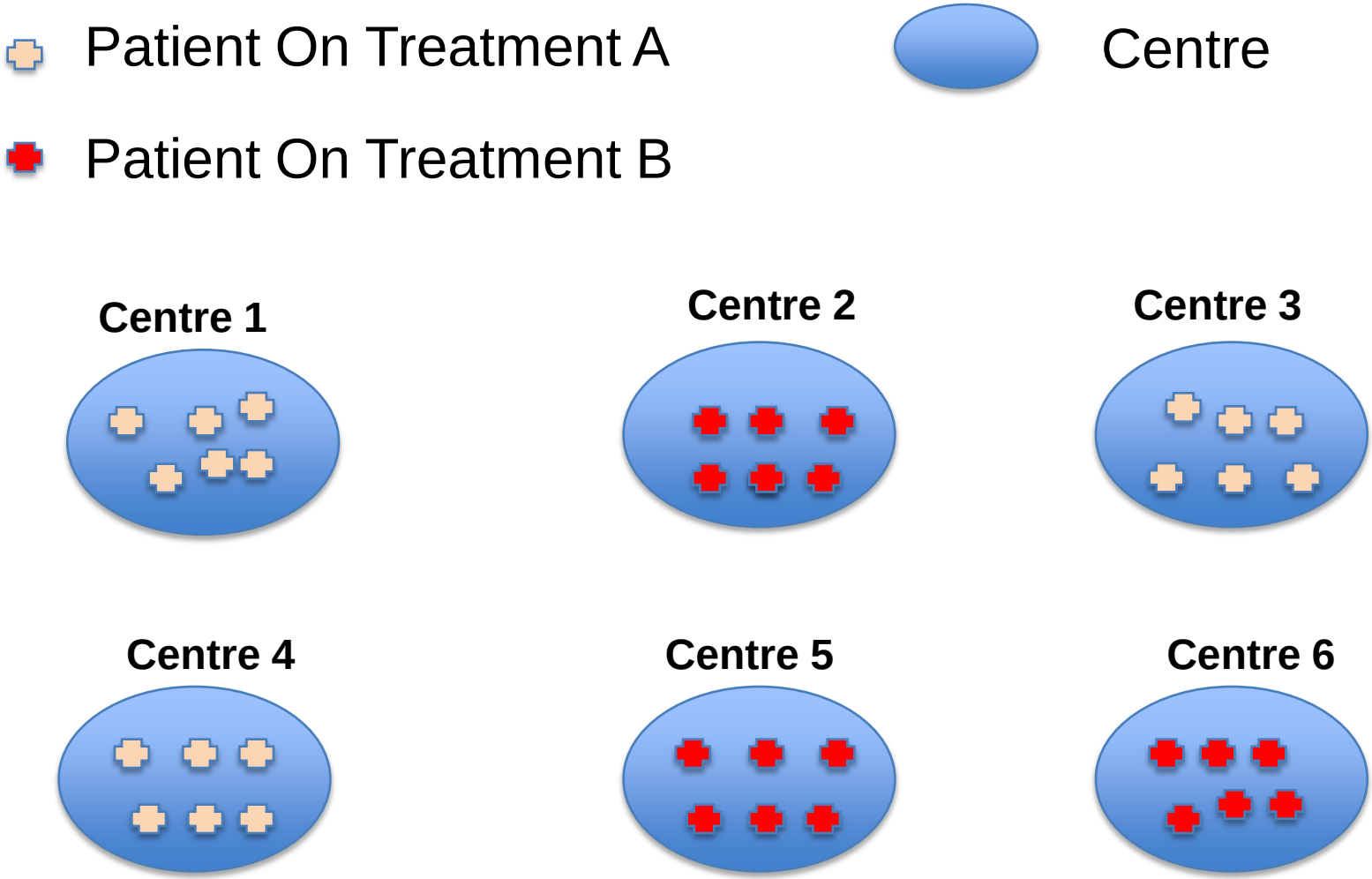
Cluster Randomized Controlled Trial (ClustRCT)

- The patients within a cluster all receive the same treatment

- The cluster is the unit of Randomization

- Different clusters receive different treatments

ClustRCT


Patient On Treatment A
Patient On Treatment B
Centre
Centre 1
Centre 2
Centre 3
Centre 4
Centre 5
Centre 6

ClustRCT Power

- The Statistical Power of a ClustRCT is generally lower than the conventional Randomized Control Trials (RCT) with the same number of patients

  - Due to the Intra-Class Correlation (ICC)

- ICC: describes how strongly patients in the same centre resemble each other

ICC Magnitude

	CENTER 1	CENTER 2	CENTER 3	CENTER 4	ICC
Infection Rate	**0.21**	**0.19**	**0.20**	**0.22**	**0**
Infection Rate	**0.30**	**0.13**	**0.24**	**0.18**	**0.014**

n = 100 for all centers

ICC Summary Statistics

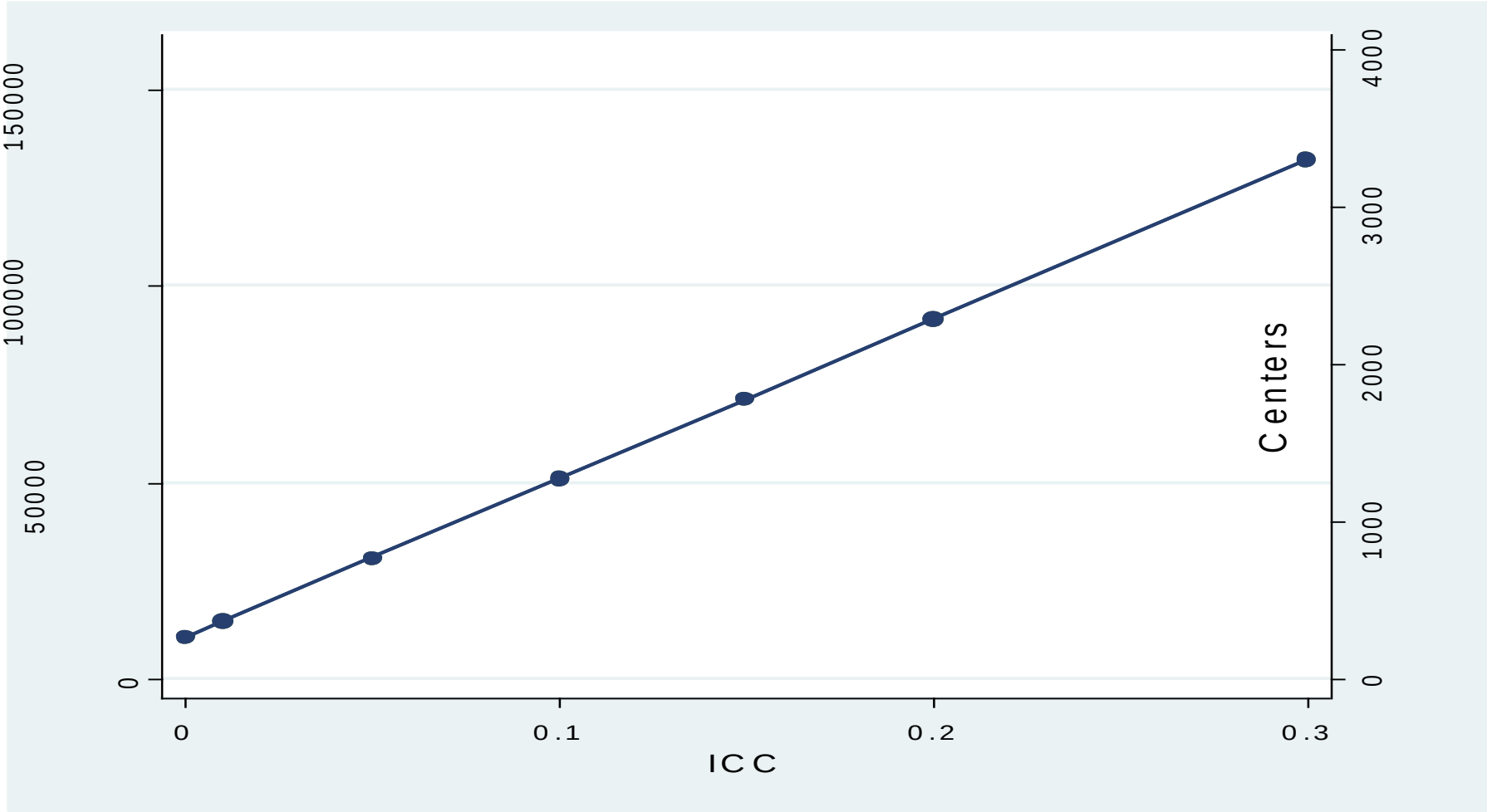
- University of Aberdeen Heath Services Research Unit have ICC database for trials with Binary outcomes
- 145 ClustRCT

Statistic	ICC
Mean	**0.084**
Min	**0**
25 Percentile	**0.012**
50 Percentile	**0.057**
75 Percentile	**0.105**
90 Percentile	**0.21**
Max	**0.659**

ClustRCT Constants

- Power = 80%
- Alpha = 0.05
- Patient per Center = 40
- Control Infection Rate = 2%
- Reduction = 35%
- Treatment Infection Rate = 1.3%

Sample Size ClustRCT Patients/Centres VS ICC



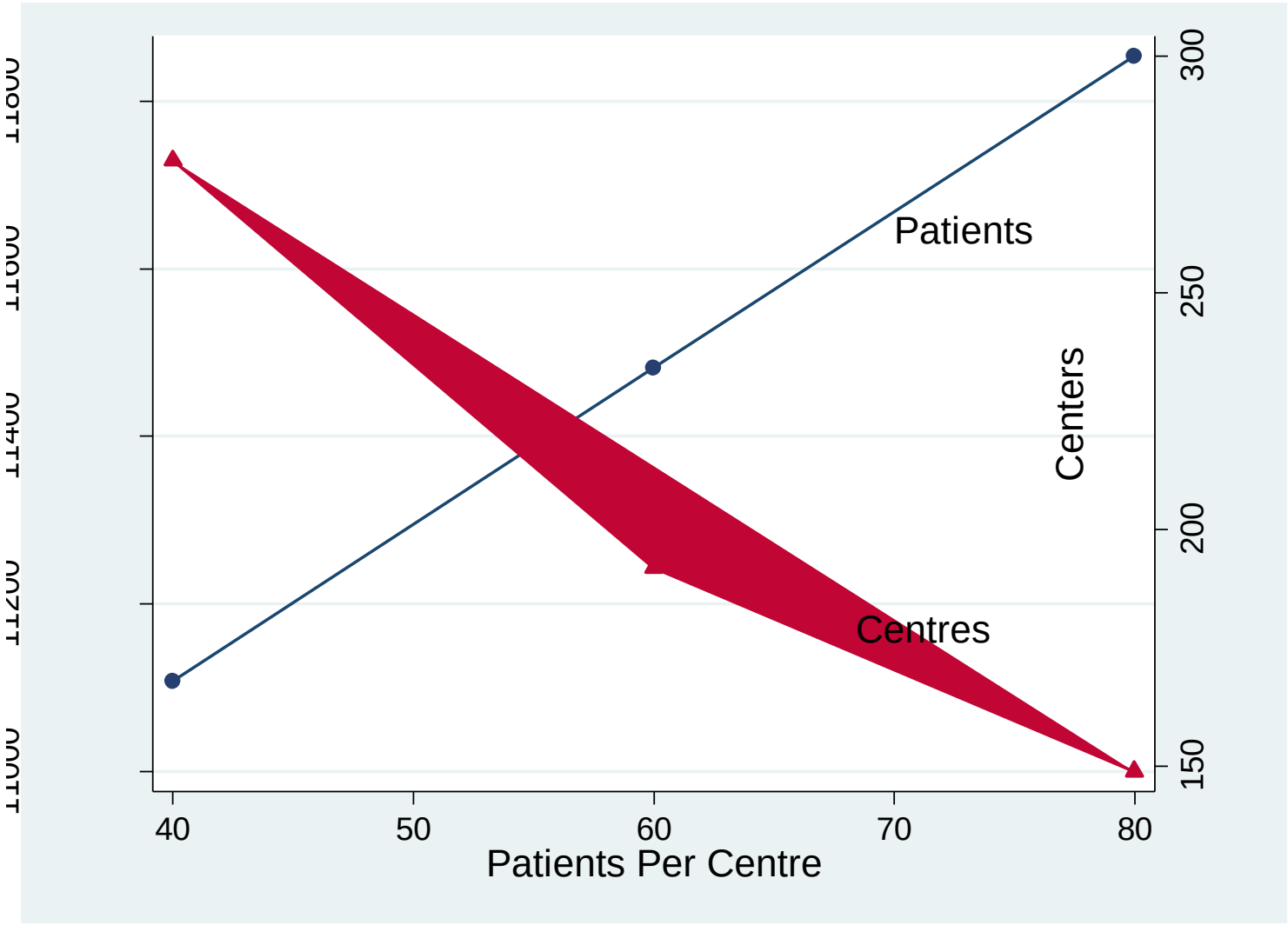
ICC Relationship

ICC	Total Patients	Centres
Increase by 0.01	Increase by 4048	Increase by 101
Increase by 0.1	Increase by 40474	Increase by 1011

Calculating ICC

- ICES (Institute of Clinical Evaluative Science)
- Had 2 years of data for 10 centres
- Provided an ICC over the 2 years = 0.0018
  - sample size of each centre not provided
- Small ICC implies a small variation in infection rate across centres

ClustPatients/Centres VS Patients Per Centre



Sample Size

Patient Per Centre	RCT		ClustRCT	
	Total Patients	Total Centres	Total Patients	Centres
40	10384	260	11108	278
60	10384	174	11482	192
80	10384	130	11854	149

Cluster Randomized Control Crossover Trial (ClustCrossRCT)

- Centres are randomized to a treatment for a set time period, then the Centre “crosses over” and all **NEW** patients receive the alternative treatment
- Centres are randomized to a treatment for a set time period, then the Centre “crosses over” and all patients **RETURN** for the alternative treatment

ClustCrossRCT

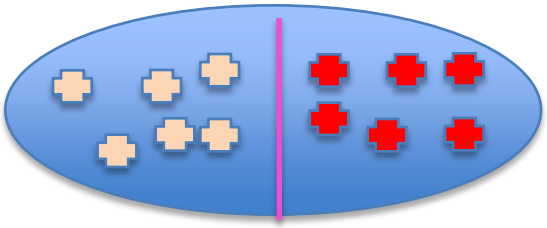
Patient On Treatment A

Patient On Treatment B

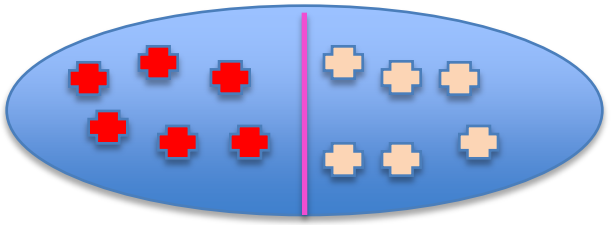
Centre

Time Period

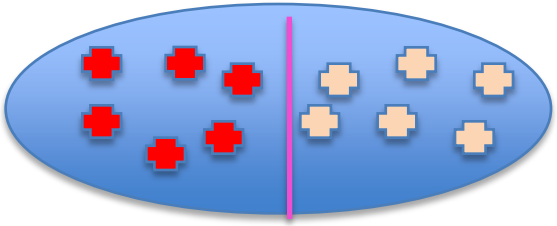
Centre 1



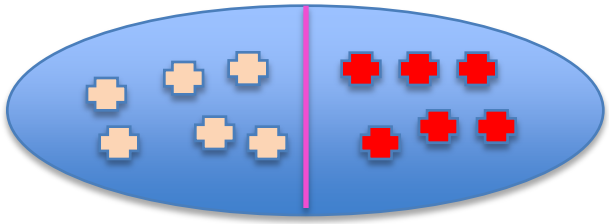
Centre 2



Centre 3



Centre 4



ClustCrossRCT

- Has Potential to reduce sample size
- Work well if intervention can easily be switched within a centre
- The centre acts as it own control
- The wash out period would be negligible
- Carry Over Effect can be measured for contamination

Sample size for ClustCrossRCT

- A formula has been derived for Continuous data

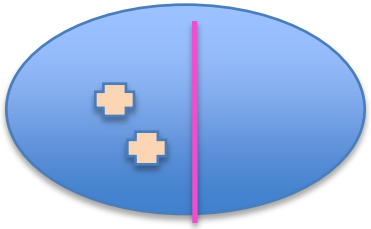
  (Giraudeau, 2008)

- For Binary Data
  - Proposed Inflation Factor for Split-Cluster Designs

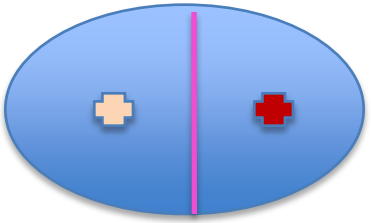
    (Donner, 2004)

ClustCrossRCT Correlations

- Clustering
  - Intra Class Correlation (ICC)
    - For any cluster, the subjects included during a period share a common correlation



- Cross-Over
  - Inter-Period Correlation (IPC)
    - Two patients included within the same cluster but at different periods share a common correlation



Calculating Correlations

– ICES (Institute of Clinical Evaluative Science)
  - Had 2 years of data for 10 centres

– Provided an ICC over the 2 years ignoring time period = 0.0018

– Treated the two years as two arms and the centres nested in each time period ICC = 0.015

(Donner & Klar)

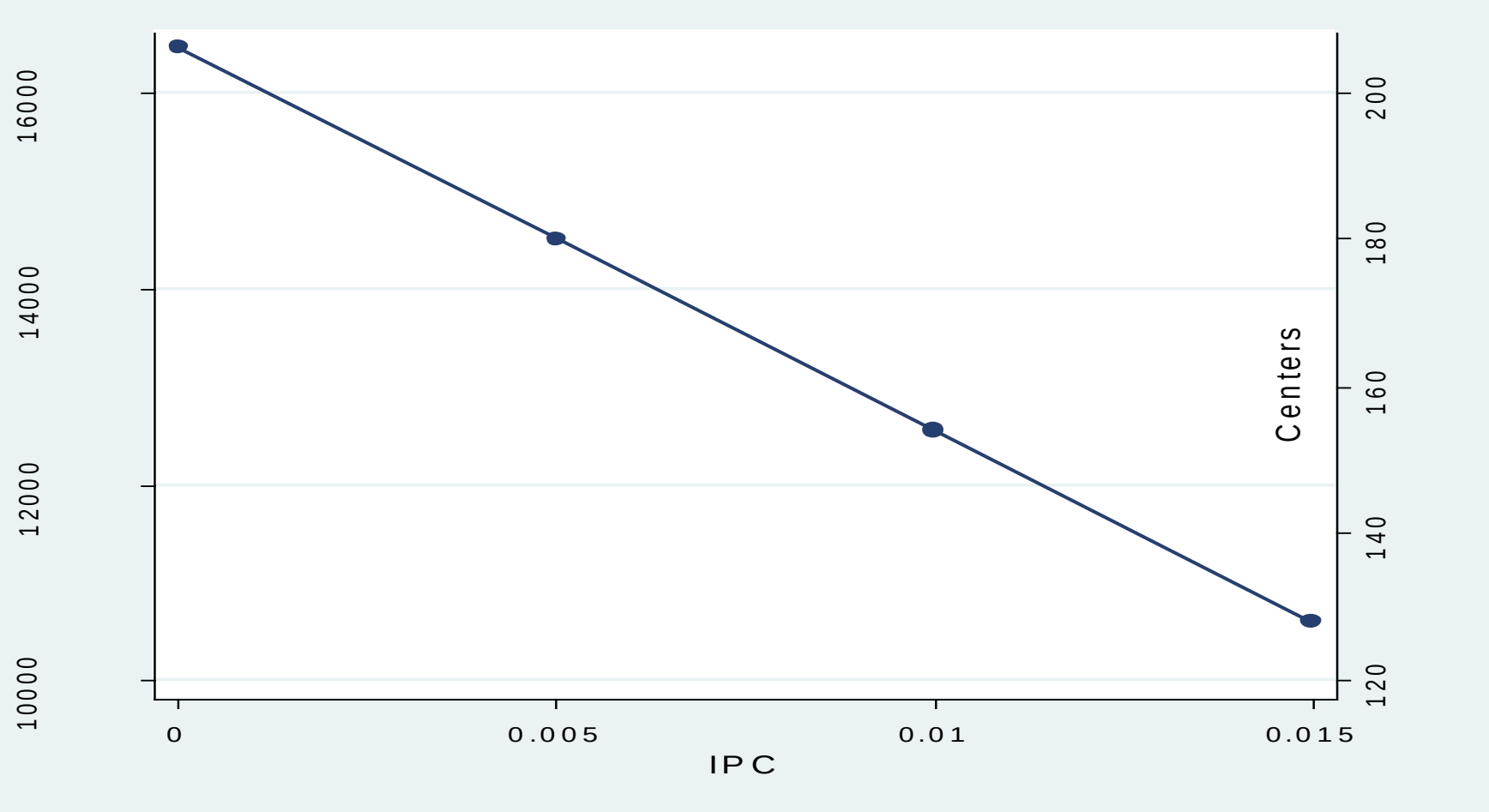
- By Defintion IPC ≤ ICC

(Turner, 2007)

CrossClustRCT Constants

- Power = 80%
- Alpha = 0.05
- Patient per Center Arm = 40
- Patient per Center = 80
- Control Infection Rate = 2%
- Reduction = 35%
- Treatment Infection Rate = 1.3%
- ICC = 0.015

ClustCrossRCT Sample Size Patients/Centres VS IPC



Sample Size Comparison

Patients Per Centre Per Treatment = 40
ICC = 0.015 IPC = 0

ClustRCT		ClustCrossRCT	
Total Patients	**Centres**	**Total Patients**	**Centres**
16450	**412**	**16459**	**206**

Sample Size Comparison

Patients Per Centre Per Treatment = 40

ClustRCT			ClustCrossRCT			
ICC	Total Patients	Centres	ICC	IPC	Total Patients	Centres
0.015	16450	412	0.015	0	16459	206
0.0018	11108	278	0.015	0.005	14382	180
			0.015	0.01	12306	154
			0.015	0.015	10229	128

Sample Size ClustCrossRCT

ICC = 0.015 IPC = 0.0075

Patients Per Treatment Per Centre	Total Patients	Centres
40	**13344**	**167**
60	**14902**	**125**
80	**165489**	**103**

Concluding Remarks

- ClustCrossRCT is a valid option when intervention is easily reversible
- Comparison between treatments within the cluster had the potential to increase statistical power
- Carry-Over effect need to be considered before Crossover trials are conducted

Future Work

- Work with ICES to obtain estimates of ICC and IPC

- Thoroughly derive a sample size formula for ClustCrossRCT for Binary data

- Explore the Inflation factor