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โรงพยาบาลศิริราช

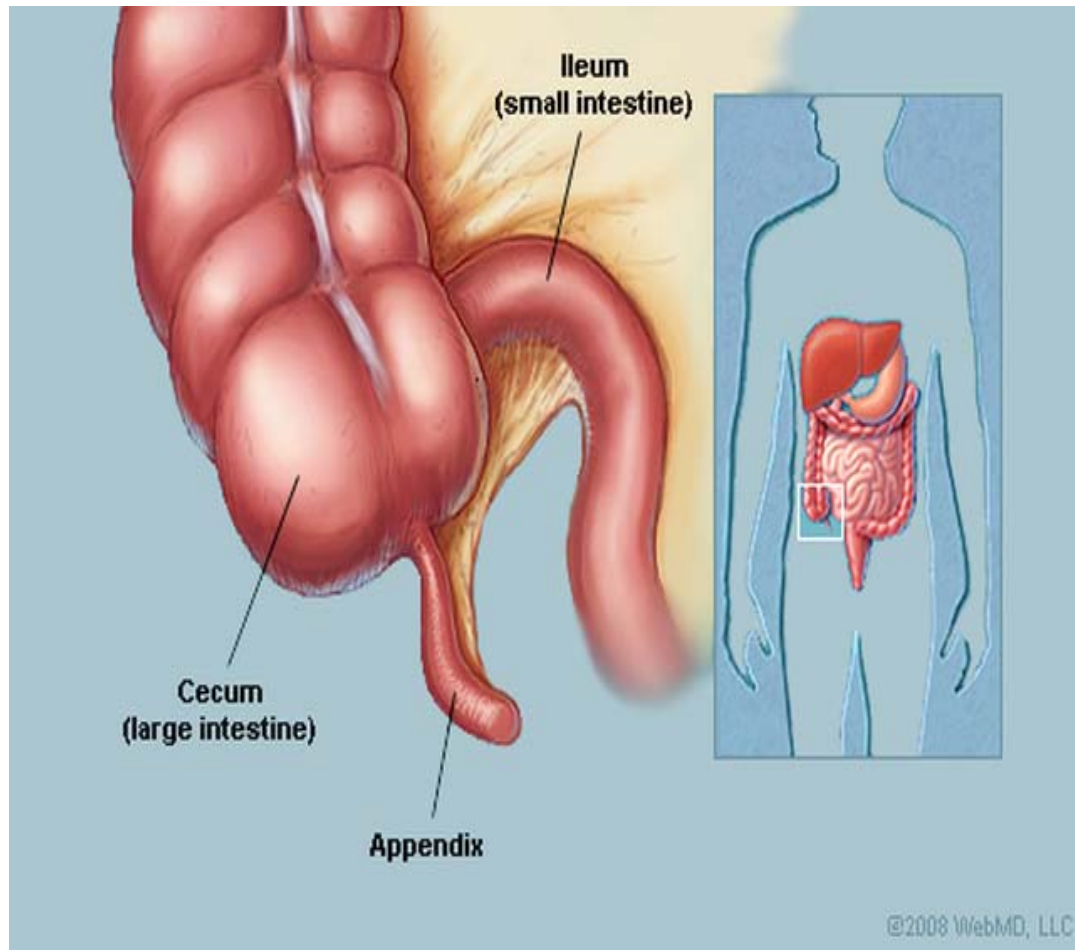
Comparison of Surgical Site Infection between Delayed Primary versus Primary Wound Closure in Complicated Appendicitis; A Multicenter Randomized Controlled Trial

Boonying Siribumrungwong, M.D., PhD.



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Introduction



Appendix

- Tubular structure
- Appendicitis is the most common surgical condition
- Pathophysiology :
Luminal obstruction



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Introduction (2)



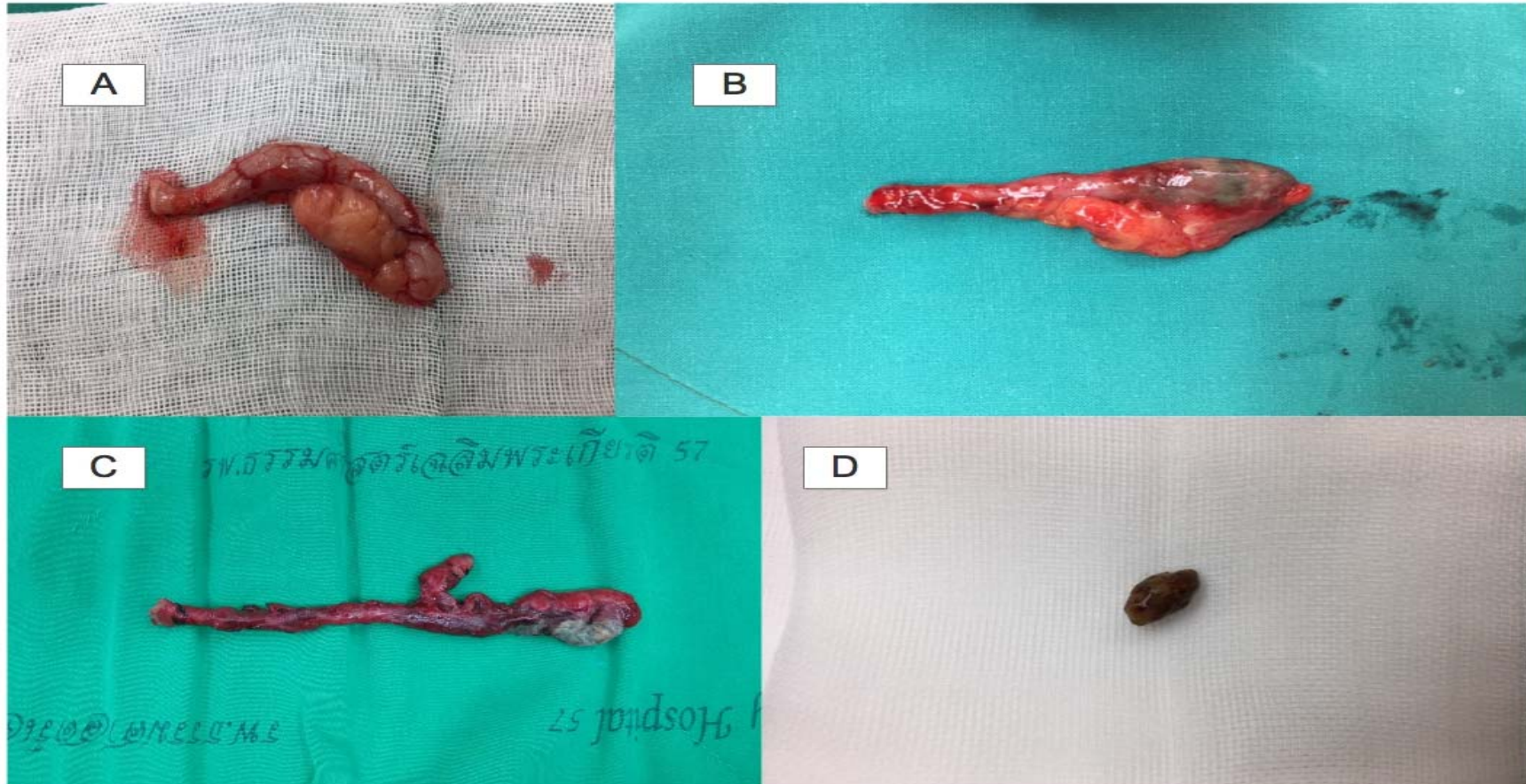
Appendicitis

- Appendectomy : standard treatment
- Through right lower quadrant incision
- McBurney's point



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Introduction (3)



Appendicitis Classification

- a) Inflamed b) gangrenous c) perforation (ruptured) d) fecolith
- Complicated appendicitis = gangrenous and ruptured
 - Associated with more complications



Introduction (4)

- Surgical site infection: most common complication after appendectomy
 - Esp. in complicated appendicitis
 - Affect both patients and healthcare provider
- In Thailand : about 20,000 ruptured appendicitis per year
 - Rate of wound infection : 10-50%
 - More nursing care, pain, length of stay, decrease quality of life
 - Increase both direct and indirect cost
 - High impact to our society



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Surgical site infection

Pathophysiology

1. Microbe related : degree of contamination, virulence of bacteria
2. Host defense mechanism : immunocompromised
3. Operative related : prolonged hospital stay, use of drain



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Type of wound closure

Primary closure (PC)

- Closed wound immediately after operation

Delayed primary closure (DPC)

- Closed 3-7 day after operation with proper wound care

Secondary intention or closure

- Dressing until wound completely healed



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Delayed Primary Wound Closure (DPC)

- Introduced since World War I in traumatic wound
- In 24-48 hr, epithelialization of primary closure
dirty incisions

- Trap bacteria, exudates, clots, and debris

Delayed primary closure (DPC)

- Effect in reducing the number of bacteria contamination and colonizing the incision
- Increase local wound resistance, tissue oxygenation, wound blood supply within 3-5 postoperative day
- Incisions closed within 5 days : same strength as primary closure

Plast Reconstruc Surg 1971; 48: 358-360



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Cons of DPC

- Daily wound dressing
 - Necessitate of resuturing
 - ? Increase pain, length of stay
 - Increase cost of treatment
-
- Considered as invasive intervention

Good research questions

From your practice, relevant question ...

And you want to know the truth

Then, you want to prove it ...

It will benefit to other patients

- S
- ?
- ?
- ?
- v

• Modern wound care

Find previous literature



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Literature review

Siribumrungwong et al. *World Journal of Emergency Surgery* 2014, **9**:49
<http://www.wjes.org/content/9/1/49>



WORLD JOURNAL OF
EMERGENCY SURGERY

REVIEW

Open Access

A systematic review and meta-analysis of randomised controlled trials of delayed primary wound closure in contaminated abdominal wounds

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Systematic review and meta-analysis

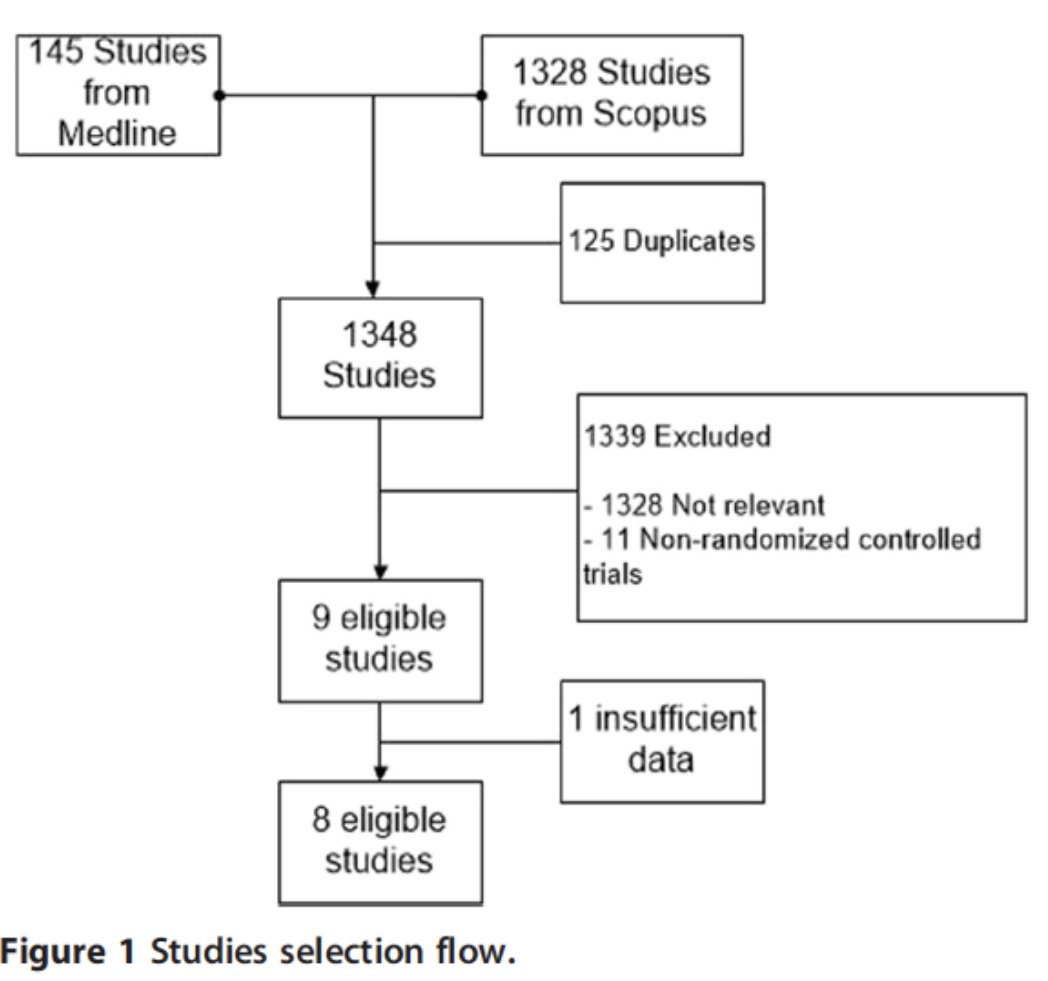


Figure 1 Studies selection flow.

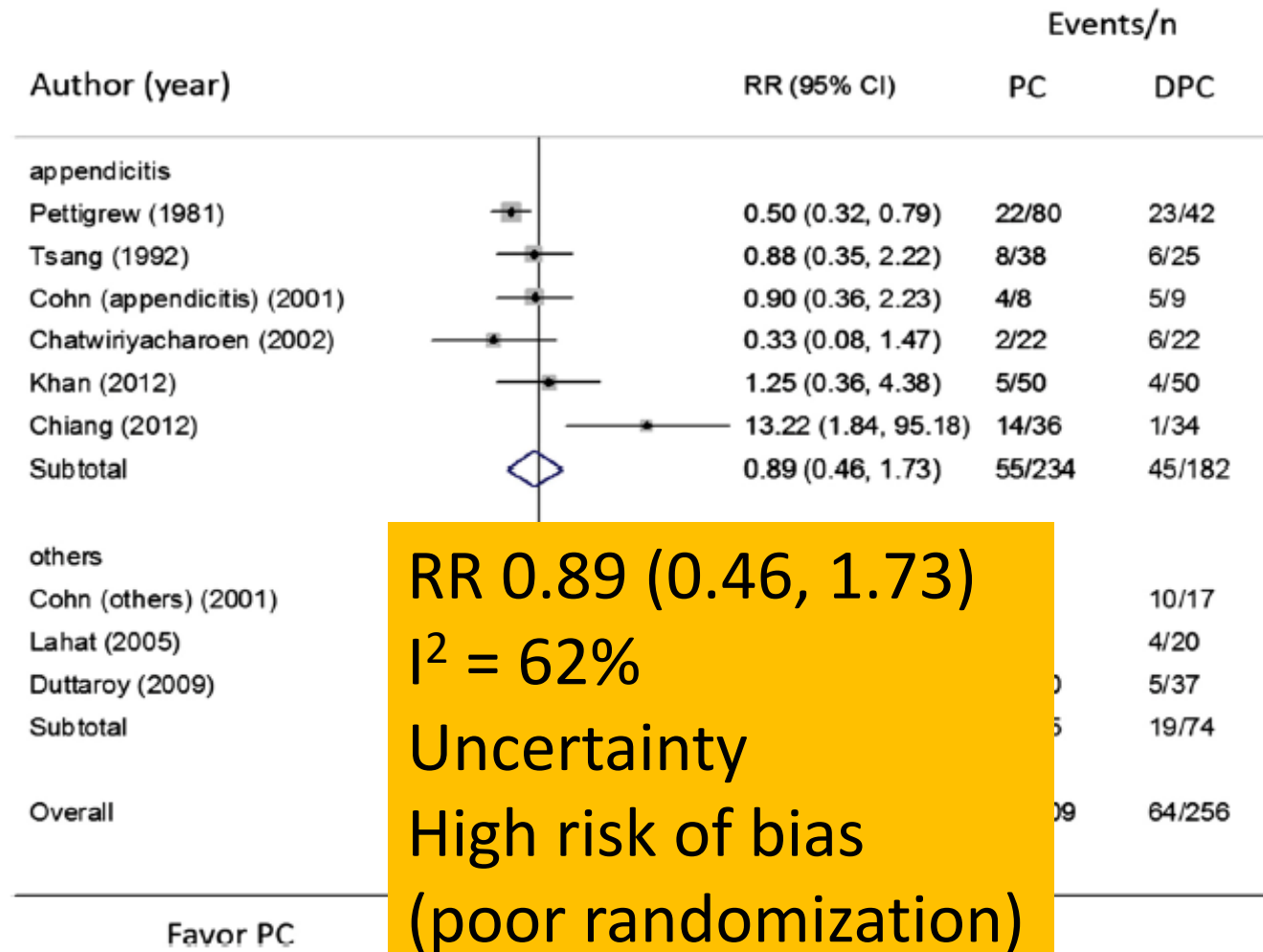


Figure 2 Forest plot of superficial surgical site infection between primary and delayed primary wound closure according to type of patients. CI, confidence interval; DPC, delayed primary closure; RR, risk ratio.



- **Wound infection**

- Increase wound dehiscence
- Increase incisional hernia
- Increase cost

- **DPC**

- Increase pain, length of stay, decrease quality of life
- Study from Canada in 1991 : DPC increased cost of up to \$400 (1,000 Bahts at that time)

(J Pediatr Surg 1991;26:1362-5)



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Research Question

Does delayed primary wound closure after appendectomy in adults with complicated appendicitis with right lower quadrant wound incision reduce postoperative superficial incisional surgical site infection compare to primary wound closure?



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Research objectives

Primary Objective

To compare the rate of postoperative superficial incisional surgical site infection in complicated appendicitis between primary and delayed primary wound closure

Secondary Objectives

- 1) To compare postoperative pain scores at days 1 and 3 after appendectomy between primary and delayed primary wound closure.
- 2) To compare quality of life at postoperative days 3 and 30 after appendectomy between primary and delayed primary wound closure.
- 3) To do cost-utility analysis between primary and delayed primary closure in complicated appendicitis



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ศูนย์การแพทย์

Why should I register my trial?

Clinical Trial Registration

The ICMJE website provides information on clinical trials and FAQs).
Briefly, the ICMJE recommends that clinical trials in a
public trial should be registered **at or before** the time of first patient enrollment
• For consider **publication**
Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance should recognize that the listing implies enforcement by the journal of ICMJE's trial registration policy.

Journals Following the ICMJE Recommendations

The following is a list of journals whose editors or publishers have contacted the International Committee of Medical Journal Editors (ICMJE) to request listing as a journal that follows the ICMJE's Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.



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Clinical trial

What is clinical trial?

- Prospective study
- Assign intervention
- With or without comparison or control group

The ICMJE defines a clinical trial as any research that involves the assignment of one or more people to an intervention, with or without concurrent comparison or control groups, to study the effect and effect relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a

Intervention-----Outcomes

- Drugs
- Surgical procedures
- Devices,
- Behavioural treatment
- Education programs, dietary interventions, Quality improvement interventions, Process-of-care changes

- Biomedical or health-related measures obtained in patients or participants

Including pharmacokinetic and adverse events



Good research questions

And equipoise

- Negotiate and convince collaborator
- It will work if you believe in that too (have faith) (relevant question + equipoise + good review data)
- This will keep your collaborator randomizing patients for you
- Other benefit ---- side paper, money ???
- Not too complicate research



Inclusion criteria

- Age > 18 year + have appendectomy with right lower quadrant incision

Operative criteria for complicated appendicitis

Gangrenous appendicitis

- Erythematous or swelling of appendix and
- Appearance of necrotic wall (dark, grayish color)

Ruptured appendicitis

- Erythematous or swelling of appendix and
- Appearance of hole in an appendix or
- Rupture of appendix during a procedure
- Appearance of frank pus



Exclusion criteria

Immunocompromised hosts

- AIDS
- History of end-stage renal disease (ESRD)
- History of autoimmune disease (SLE)
- Taking immunosuppressive agents (prednisolone, methotrexate, cyclophosphamide, azathioprine, mercaptopurine, anthracycline, mitomycin, Ciclosporin, Tacrolimus)
- Cirrhosis with ascites
- Morbid obesity (BMI > 40 kg/m²)



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Randomization

- Ratio 1:1
- **Stratified block randomization based on study site**
- Vary block size of 4 to 6
- Sequence generation : independent statistician
- Allocation concealment : sequential sealed opaque envelope
 - Open : met intraoperative criteria
 - **Before skin closure**



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Blinding

- Primary outcome
 - Not blinded
 - Standard operative procedure for measure outcome
- Research assistant
 - Secondary outcomes (pain, recovery time, quality of life, cost)
 - blinded



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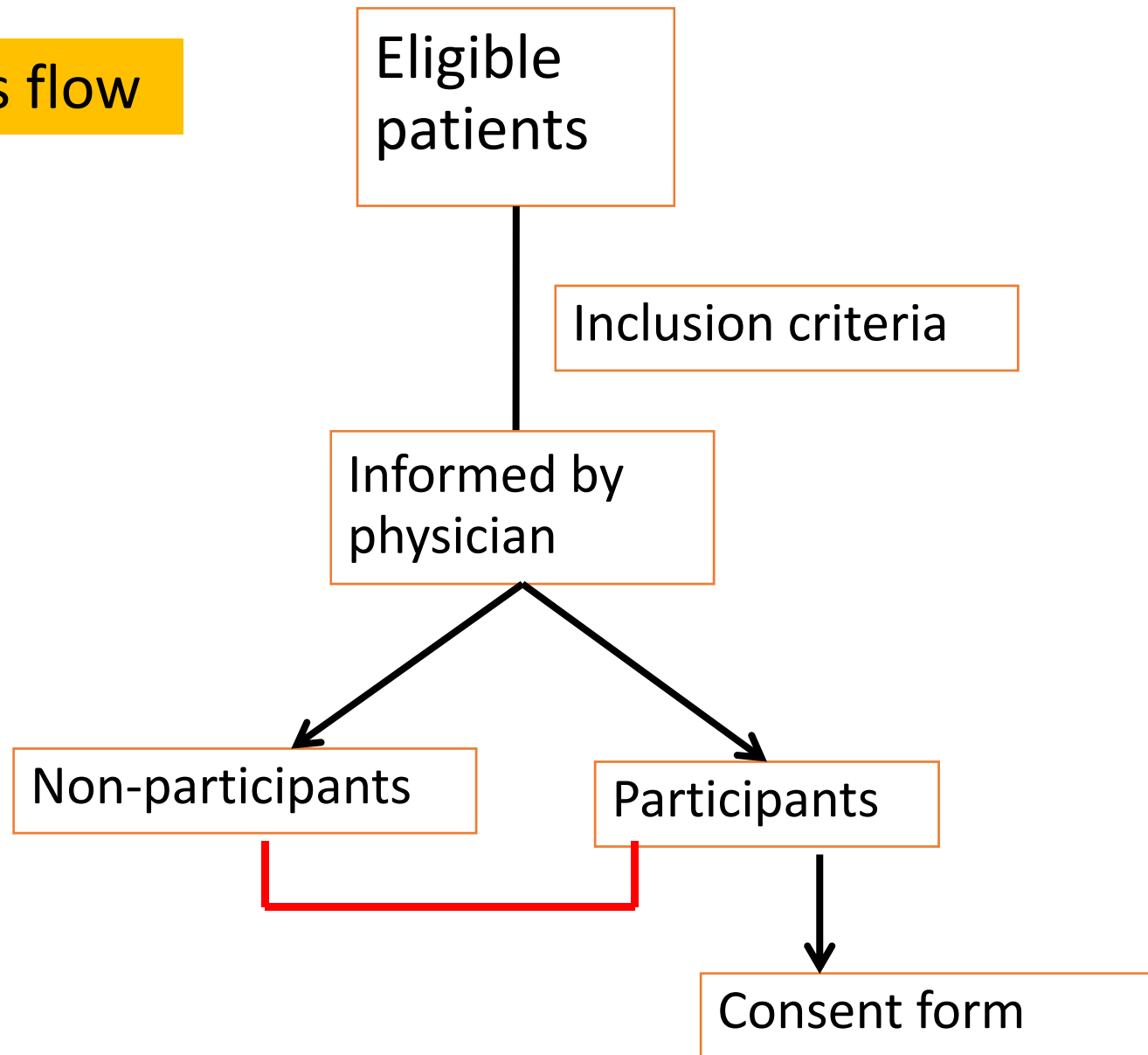
Co-intervention

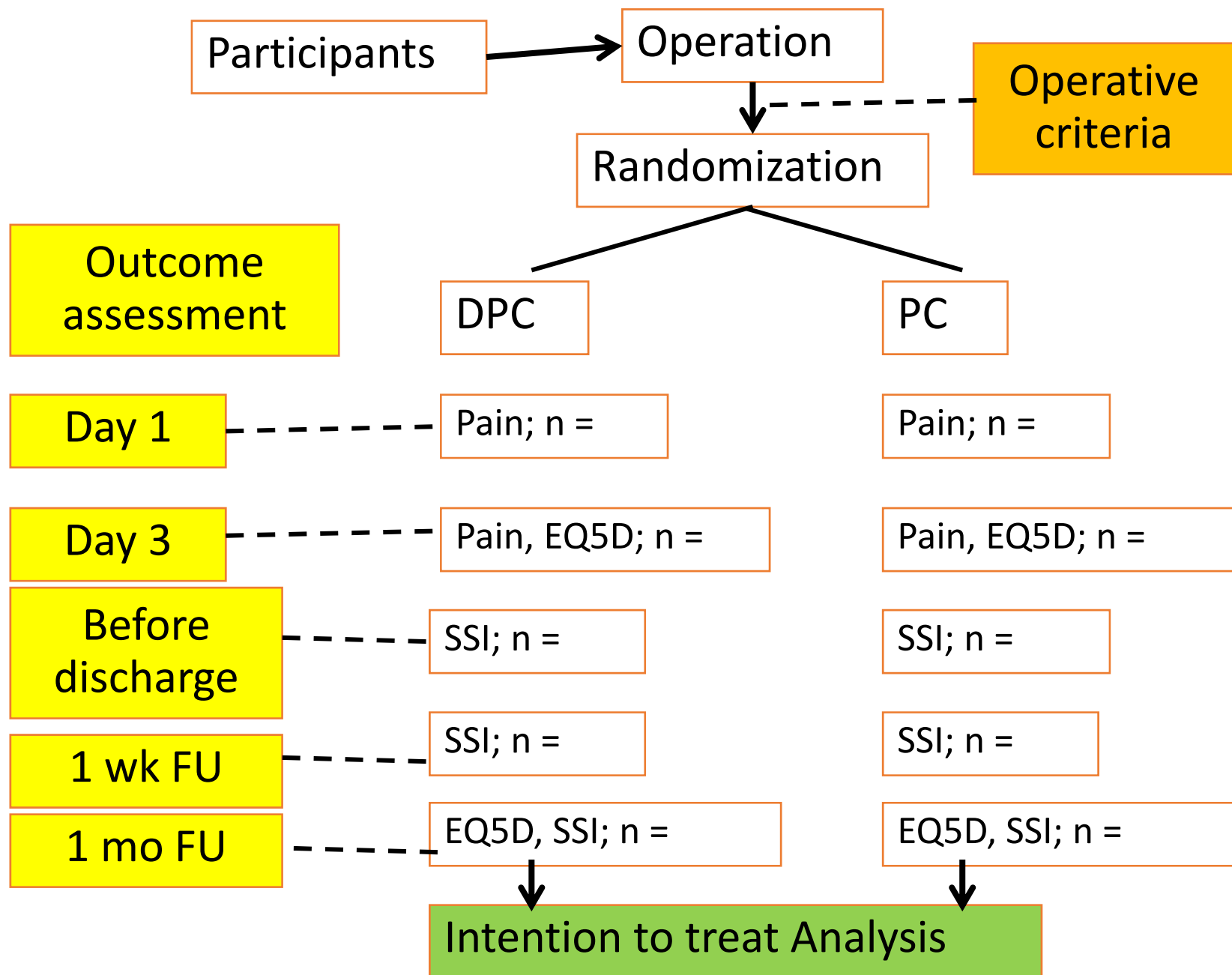
- Perioperative antibiotics
 - Postoperative pain control
 - Wound dressing and care
- Important co-intervention = major confounder to the outcomes
 - Meeting and consensus between all collaborator



- Superficial surgical site infection
 - CDC criteria
- Postoperative pain : VAS (100 mm scale)
- Recovery time
 - Times to return to normal activities (day)
 - Times to return to work (day)
- Quality of life
 - EQ5D (5 scale) ----- convert to utility scores
- Costs
 - Direct medical costs : assume equal except cost of wound care (dressing and resuture)
 - Direct non-medical cost and indirect cost : interview

Patient's flow







Sample size estimation

- Pooled rate of SSI in DPC = 29.5 (95%CI:14.8, 44.2)
- Type I error = 0.05
- Power = 0.8
- Ratio 1:1
- Test for difference (two-sided)
- Size of detectable = 10%
- 285 / group ----- 570 + 5% loss FU
----- **600**



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Data analysis

- Intention to treat analysis
- Primary outcomes
 - Binary regression analysis with or without adjusted variable
 - Protocol violation : Per-protocol, as-treated, counterfactual
 - Imputed data
- Secondary outcomes
 - Mixed linear regression model
- Cost-utility analysis
 - Incremental cost-effectiveness ratio (ICER)



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Results

- 607 patients
 - 126 Thammasat University
 - 92 Ramathibodi
 - 117 Chonburi
 - 30 Pathum tani
 - 170 Lampang
 - 72 Surin



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Consort flow diagram

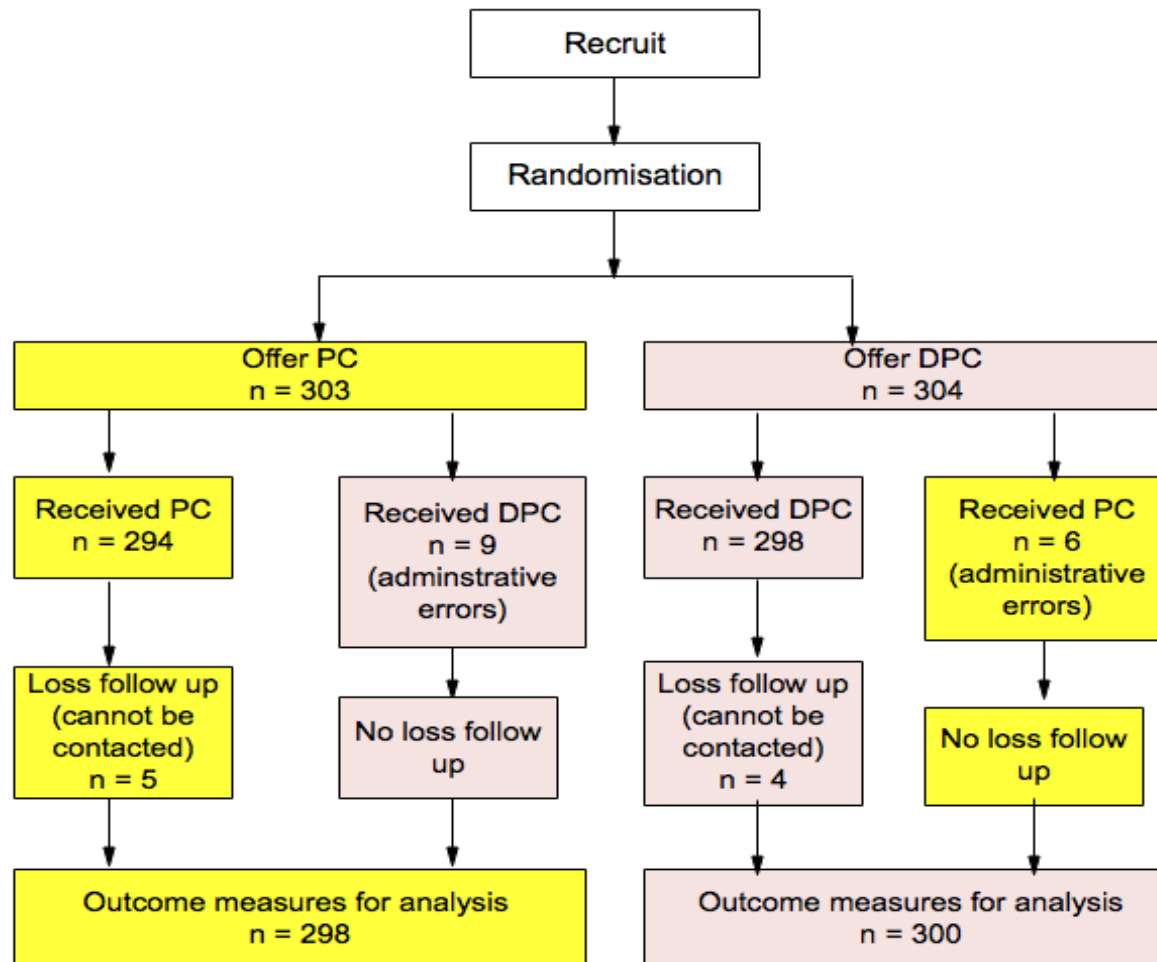
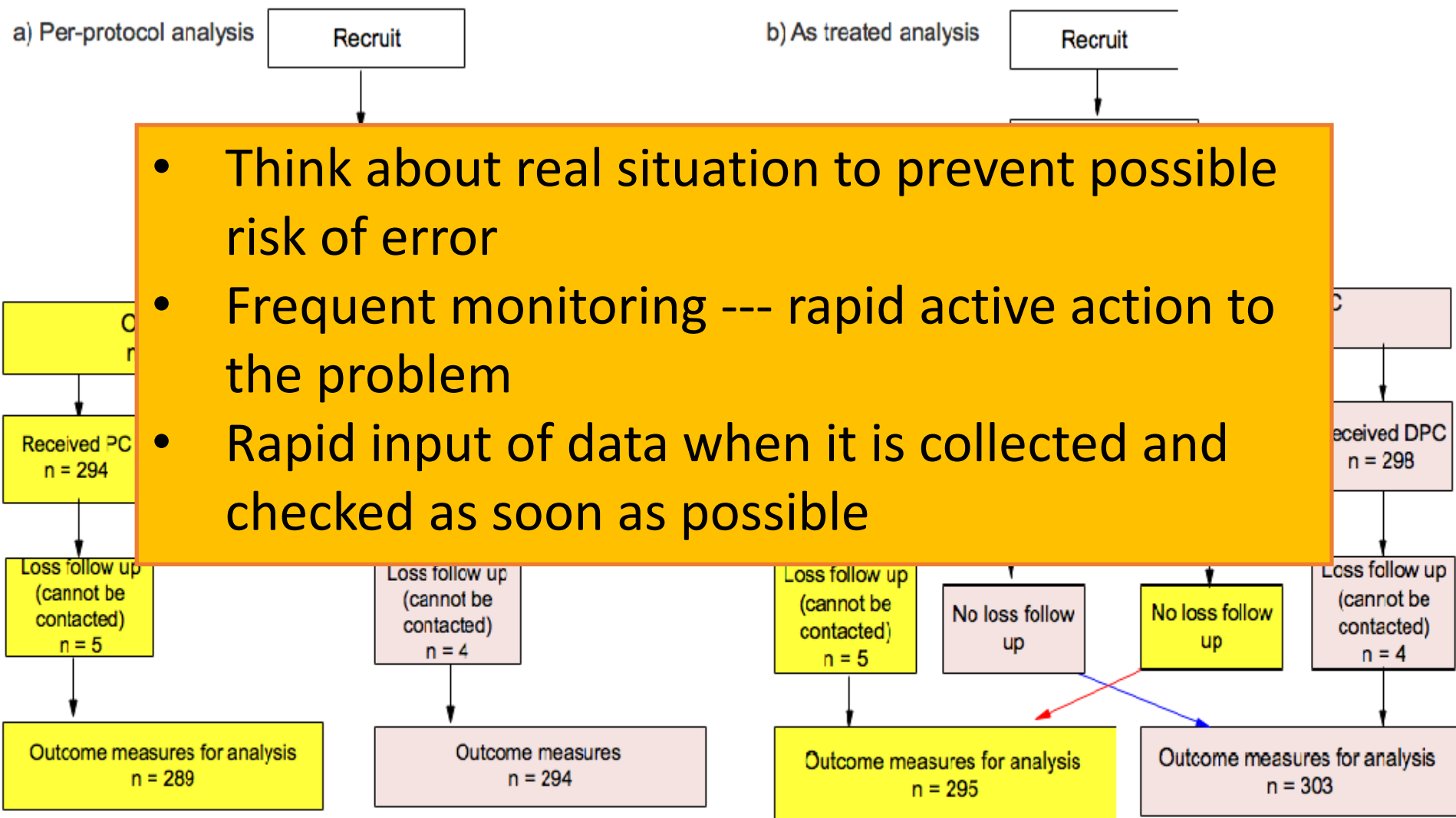


Figure 1. Consort flow diagram



- Think about real situation to prevent possible risk of error
- Frequent monitoring --- rapid active action to the problem
- Rapid input of data when it is collected and checked as soon as possible

c) Instrumental variable analysis

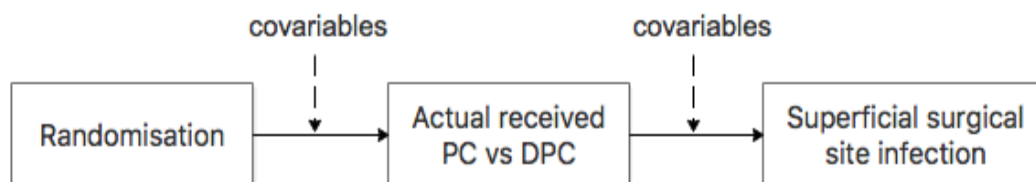


Figure 2. Different approaches analysis. a) Per-protocol analysis b) As treated analysis c) Instrumental variable analysis

Characteristics	DPC (n = 304)	PC (n =303)
Age , years, mean (SD)	46 (18.0)	45 (18.1)
Gender, number (%)		
Male	155 (51)	169 (56)
Female	149 (49)	134 (44)
BMI , kg/m ² , mean (SD)	23.4 (4.31)	23.4 (4.34)
Smoking, number (%)	45 (15)	51 (17)
ASA classification, number (%)		
Class I + II	266 (89)	257 (85)
Class III + IV	34 (11)	44 (15)
Diabetes, number (%)	31 (10.3)	20 (6.7)
Hypertension, number (%)	55 (18.2)	60 (20)
Symptom onset, hours, mean (SD)	24 (15, 18)	24 (14, 18)
White blood cell count , cell/mm ³ , mean (SD)	15561 (4965)	15790 (4979)
Body temperature , °Celsius, mean (SD)	37.7 (1.0)	37.7 (1.1)
Fever, number (%)		
≥ 37.8 °Celsius	142 (47)	148 (49)
< 37.8 °Celsius	159 (53)	154 (51)
Preoperative utility, median (IQR)	0.68 (0.34, 0.80)	0.68 (0.34, 0.80)
Operative time, minutes, median (IQR)	47 (14, 74)	51 (18, 78)
Operative time classification, number (%)		
≤ 75 percentile (< 77 minutes)	232 (77)	222 (74)
>75 percentile (≥ 77 minutes)	68 (23)	80 (26)



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Baseline characteristics (2)

Characteristics	DPC (n = 304)	PC (n =303)
Used of drain, number (%)	62 (20.6)	58 (19.2)
Severity, number (%)		
Gangrene	76 (25)	72 (24)
Ruptured	228 (75)	231 (76)
Intraoperative rupture	23 (7.6)	20 (6.6)
Visible wound contamination, number (%)		
Exudative fluid	81 (27)	87 (29)
Pus	118 (39)	108 (36)
Feculent material	38 (13)	38 (13)



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SSI

- 9 miss outcomes
- 52 superficial SSIs
- 8.7% (95%CI: 6.7, 11.2)
- 88% diagnosed in 1 week FU, 12% at 1 month FU

Approach	DPC	PC	RR (95%CI)	RD (95%CI)	P value
ITT					
N	300	298	0.74 (0.44, 1.25)	-0.026 (-0.071, 0.019)	0.258
Rate (% , 95%CI)	10 (6.6, 13.3)	7.3 (4.4, 10.3)			
PP					
N	294	289	0.74 (0.44, 1.25)	-0.026 (-0.071, 0.019)	0.411
Rate (%)	10 (6.6, 13.3)	7.3 (4.4, 10.3)			
AT					
N	294	289	0.74 (0.44, 1.25)	-0.026 (-0.071, 0.019)	0.632
Rate (%)	10 (6.6, 13.3)	7.3 (4.4, 10.3)			
IV					
N	294	289	0.74 (0.44, 1.25)	-0.026 (-0.071, 0.019)	0.243
Rate (%)	10 (6.6, 13.3)	7.3 (4.4, 10.3)			
IV(with adjusted variables)					
N	276	282	0.66 (0.30, 1.01)	-0.036 (-0.083,0.011)	0.118
Rate (% , 95%CI)	10.7 (7.0, 14.1)	6.9 (4.1, 9.8)			

DPC --- 10 %

PC --- 7.3%

RR = 0.74 (0.44, 1.25)



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Discussion

- Rate of SSI between DPC and PC
 - Not different
- Length of stay, recovery time, postoperative pain, and QoL
 - Not different
- Less cost in PC : ~ 2100 Baht/case



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Discussion

- Approaches
 - Increase robustness of the results
 - Different approaches
 - Per-protocol : selection bias
 - As-treated : observational studies (randomisation broke)
 - Counterfactual : complier average causal effect (CACE)
 - ITT : policy maker (equal proportion of nonadherence in studies and in population), clinical practice guideline
 - CACE : clinician recommendation for complied patients



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Cost-effectiveness

- $ICER = [cost(A) - cost(B)] / [QALY(A) - QALY(B)]$
- With increase cost with no benefit and QALY gain
- Not cost-effectiveness (dominated)



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Impact of studies

- PC saves 2083 Baht/case over DPC
- 65,729,098 population in mid 2015
- Estimated incidence of appendicitis of 14/10000 pop/year = 92020 appendectomy/year
- With 18.2% = complicated appendicitis
 - 16,748 complicated appendicitis / year
 - Apply PC in every case :--- **saves 34,886,084 Baht /year**



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Conclusion

PC is not different comparing to DPC in adults with complicated appendicitis (i.e. gangrenous and ruptured) with lower costs



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Thank you

- Team approach
- Good mentor
- Good collaborator
- Your mind --- face the problem, don't give up, be patience, happy with it --- successful

Dimension		UK	Thai
Constant		0.081	0.202
Mobility	Level 1	0	0
	Level 2	0.069	0.121
	Level 3	0.314	0.432
Self care	Level 1	0	0
	Level 2	0.104	0.121
	Level 3	0.214	0.242
Usual activities	Level 1	0	0
	Level 2	0.036	0.059
	Level 3	0.094	0.118
Pain/discomfort	Level 1	0	0
	Level 2	0.123	0.072
	Level 3	0.386	0.209
Anxiety/depression	Level 1	0	0
	Level 2	0.071	0.032
	Level 3	0.236	0.11
N3		0.269	0.139

Utility from
EQ-5D

Sakthong P. Measurement
of clinical-effect: utility.
J Med Assoc Thai. 2008
Jun;91 Suppl 2:S43-5



- Direct cost
 - Direct medical costs
 - Cost of goods and services that are directly provided by the health care system
 - Hospital days, drugs, home nursing
 - Direct non-medical costs
 - Costs of goods and services used for health care that are not directly provided by the health care system
 - Informal care, transportation



- Indirect cost
 - Indirect non-medical costs
 - The value of production loss due to illness or treatment
 - Income lost from sick-leaved



- Infection occurs within 30 days after the operative procedure and
- Involves only skin and subcutaneous tissue of the incision and
- One of the following
 - Purulent drainage from the superficial incision.
 - Organism isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
 - At least one of the following signs or symptoms: pain or tenderness; localized swelling, redness, or heat And the superficial incision is deliberately opened by surgeon (A negative culture does not meet this criterion)