

Design and Analysis Issues In Knowledge Translation Trials in Primary Care

Lehana Thabane, PhD
Clinical Epidemiology and Biostatistics

For
CANNecTIN Program
January 9, 2009



Issues

- **Issue #1: Randomization Process**
 - Unit of randomization: Patient vs Physician vs Practice
 - Dealing with potential clustering effect
 - Enhancing physician or practice participation
- **Issue #2: Choice of Primary outcome**
 - Process vs clinical outcome
 - Individual vs composite outcome/score
 - Single vs multiple/multivariate outcomes

Issues

- **Issue #3: Data Collection**
 - Balancing the research needs vs uninterrupted patient care – being pragmatic
- **Issue #4: Sample size calculation - Method of analysis**
 - Unit of analysis vs unit of randomization
 - Accounting for clustering effect
 - Optimal choice of method of analysis

Illustrative Example

COMPETE

(Computerization of Medical Practices for
the Enhancement of Therapeutic
Effectiveness)

<http://www.compete-study.com>

COMPETE III Team

- **Investigators**

- Dr Anne Holbrook (PI), Dr Bob Bernstein, Dr David Chan, Dr Greg Curnew, Dr Catherine Demers, Dr Lisa Dolovich, Dr Hertzell Gerstein, Dr Dereck Hunt, Dr Karim Keshavjee, Dr Victor Montori, Dr Lehana Thabane

- **Staff**

- Sue Troyan (research coordinator)
- Several others: research assistants/data abstractors/site coordinators/students/data analysts

Background

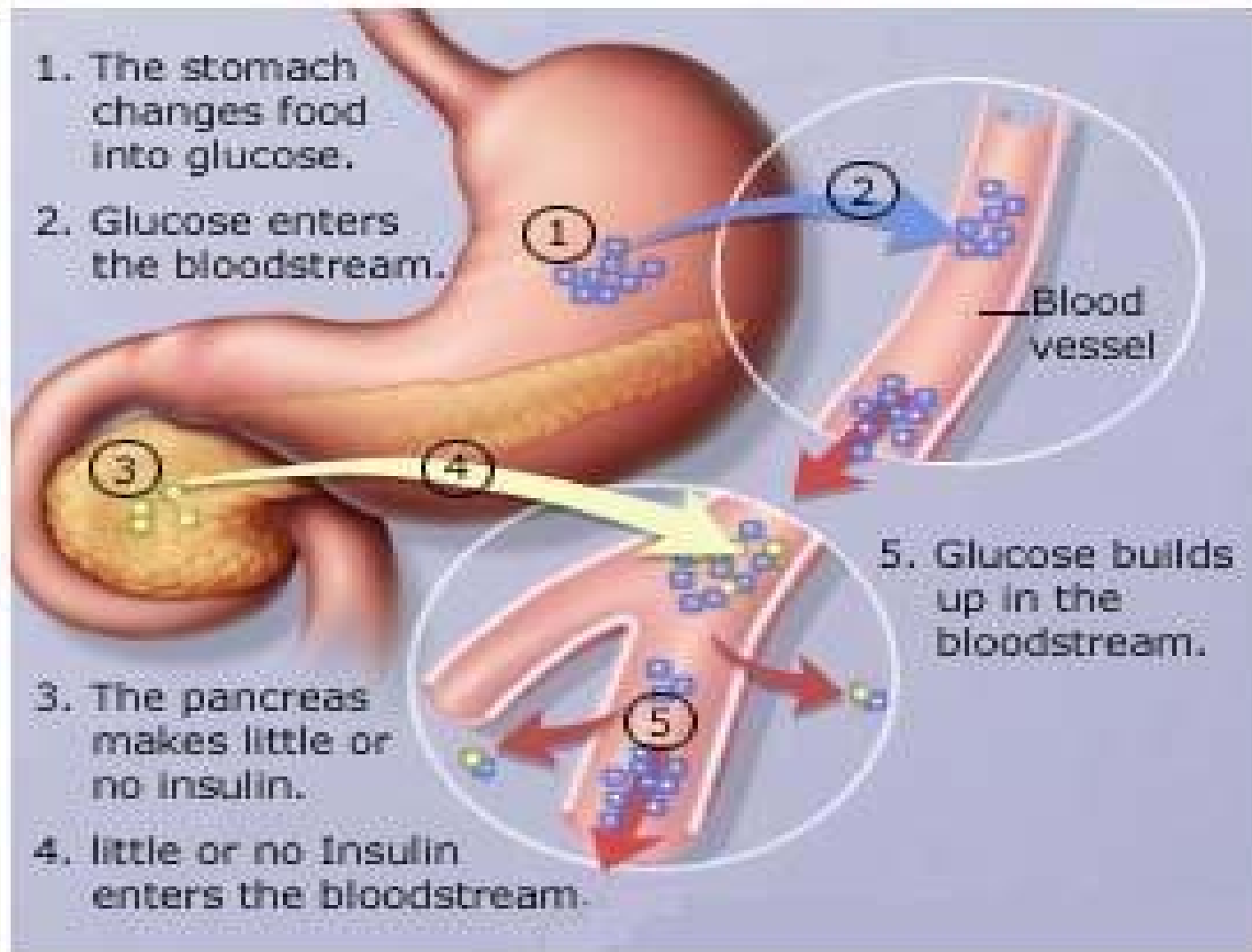
- Diabetes is a complex chronic disease with multiple risk factors
- It leads to serious complications
 - Heart disease
 - High blood pressure
 - Eye problems
 - Foot problems
 - Hyperglycemia – high blood sugar
 - Hypoglycemia – low blood sugar
 - Skin problems

Background

- Type 1 Diabetes
 - Body's immune system destroys insulin-producing cells in the pancreas
- Type 2 diabetes
 - Combination of too much insulin (insulin resistance) and too little or no insulin (insulin deficiency)
 - Affects 90-95% of diabetes patients
 - Has modifiable risk factors

Diabetes Image

(www.generalhealthinfo.wordpress.com)



Background

- In Canada, primary care practitioners play an important role in management of patients with chronic conditions
- Use of Computer Decision Support Systems (CDSS) in primary care is increasing
- COMPETE I showed that it feasible to develop and implement CDSS in primary care

COMPETE II (An RCT)

(Manuscript prepared for re-submission to CMAJ)

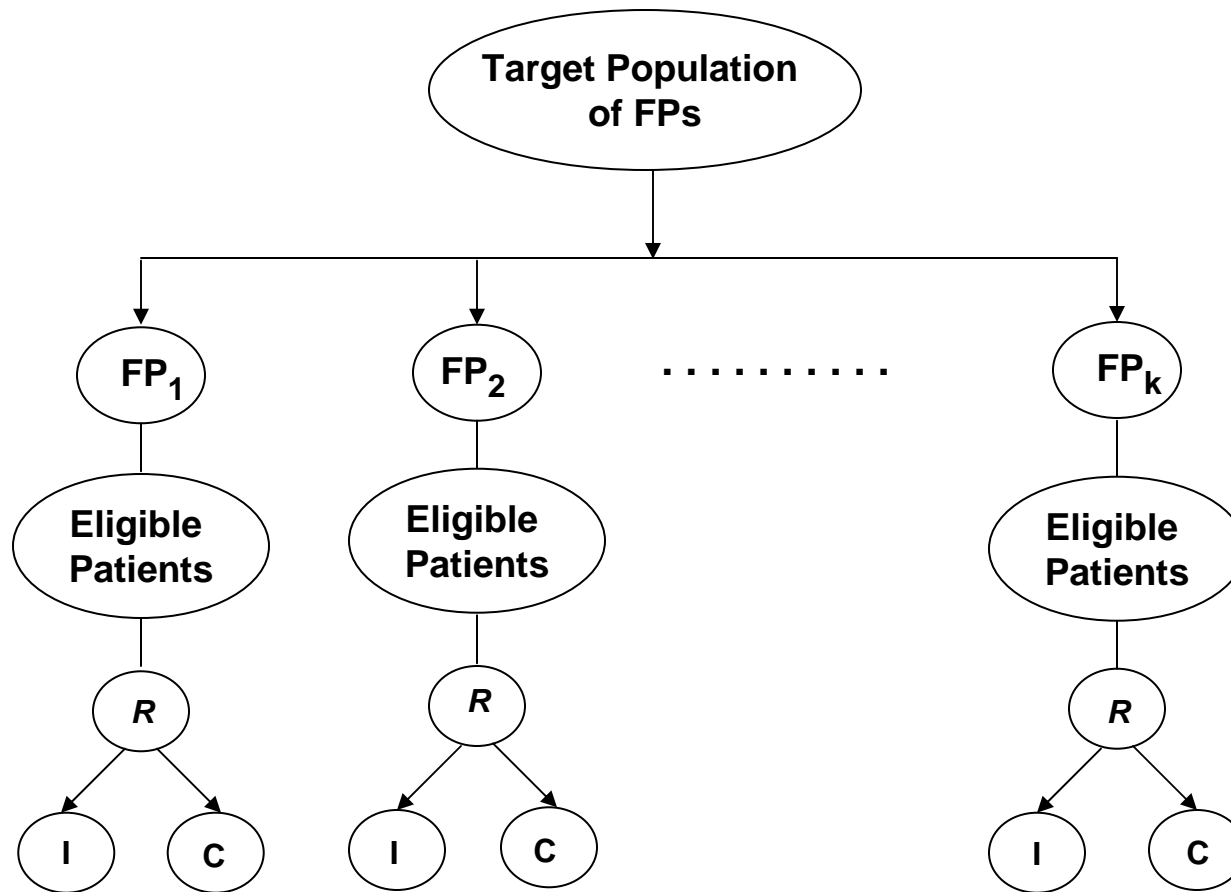
- To develop an effective, integrated clinical decision-support tool for patients and health care providers
- To develop and test a diabetes tracker as a model for evidence-based chronic disease management
- To evaluate whether an individualized diabetes tracker linked to an electronic medical record (EMR) compared with usual care can improve the quality of management of diabetes in primary care

COMPETE III (RCT)

(Analysis currently underway)

- Broadened to vascular risk, - diabetes, hypertension, cholesterol, previous heart attack or stroke
- Expanded beyond patients and primary care providers to include specialists and clinical care coordinators

COMPETE II & III Trials



Vascular Tracker
 Risk Calculator

Site ID: 11 MD: 2 - Dr. [redacted] [Show Page Size](#)
 Patient: [redacted] [Printable page](#)

Known Vascular Risks and History: no MI no Diabetes
 Yes CAD Yes Hypertension
 no PVD no Stroke Yes Hypercholesterolemia

	Patient Status		Target Value & Interval	Information & Recommendation
	Previous	Most recent		
FP Visit	2005-Jul-26 <i>2005-Jul-26</i>	2005-Nov-22 <i>2005-Nov-22</i>	3 mo.	Resources Advice
A1c	0.054 <i>2005-Nov-17</i>	0.056 <i>2006-Mar-04</i>	< 0.07 3-6 mo.	Resources Advice
Blood Pressure	128/70 <i>2005-Jul-26</i>	142/80 <i>2005-Nov-22</i>	< 140/90 3 mo.	Resources Advice Recommended Meds
LDL-cholesterol	3.94 <i>2005-Mar-14</i>	3.75 <i>2006-Mar-04</i>	< 2.5 mmol/L 6-12 mo.	Resources Advice
Smoking	0 cigs/day <i>2005-Nov-04</i>	0 cigs/day <i>2006-Feb-17</i>	0 cigs/day 3 mo.	Resources
Weight	38 kg/m2 <i>2005-Apr-05</i>	38 kg/m2 <i>2005-Apr-13</i>	< 25 kg/m2 Target wt.=69kg / <102 cm / <0.95 3 mo.	Resources Advice
Diet	5 fruits&vegs/day <i>2005-Nov-04</i>	5 fruits&vegs/day <i>2006-Feb-17</i>	>=4 fruits&vegs/day 3 mo.	Resources Advice
Exercise	240 <i>2005-Nov-04</i>	240 <i>2006-Feb-17</i>	> 240 min/wk 3 mo.	Resources Advice
Psychosocial	No Problem <i>2005-Nov-04</i>	No Problem <i>2006-Feb-17</i>	No Problem 3 mo.	Resources
ASA/Antiplatelet	Taking <i>2005-Jul-26</i>	Taking <i>2005-Nov-22</i>	Taking 3 mo.	Resources Advice
Urine albumin (ACR/24hr UAE)	Not available <i>Not available</i>	0.5 g/mol Cr <i>2005-Mar-14</i>	<2.0g/mol Cr <30mg/24hr 12 mo.	Resources Advice
Eye exam	Not applicable <i>Not applicable</i>	Not applicable <i>Not applicable</i>		Resources
Foot exam	Not applicable <i>Not applicable</i>	Not applicable <i>Not applicable</i>		Resources
Flu shot date	Not up-to-date <i>Not applicable</i>	Not applicable <i>Not applicable</i>	12 mo.	Resources
Medication Adherence	Adherent <i>2005-Nov-04</i>	Adherent <i>2006-Feb-17</i>	Adherent 3 mo.	Resources

Clinforma - Vascular Tracker for COMPETE III - Windows Internet Explorer

https://www.clinforma.net/COMPETE3/CCCVTDemo/(hfaysbqqz) Search Google

File Edit View Favorites Tools Help

Clinforma - Vascular Tracker for COMPETE III

COMPETE **Vascular Tracker** for COMPETE III Powered by **clinforma.NET** Logout

User ID: [redacted] Patient ID: [redacted] Last updated on: 2006-Apr-11, 08:19

Patient Practice Resources Messages

Vascular Tracker Risk Calculator

Site ID: 11 MD: 2 - Dr. [redacted]

Patient: [redacted]

Known Vascular Risks and History:

no MI	no Diabetes
Yes CAD	Yes Hypertension
no PVD	no Stroke
	Yes Hypercholesterolemia

* Risk of a cardiovascular event calculated below represents only part of the total risk of all vascular events, which also include stroke and peripheral vascular disease.
 * The risk calculation also assumes no diabetes and no previous heart attack or stroke. Otherwise, actual risk is likely higher.

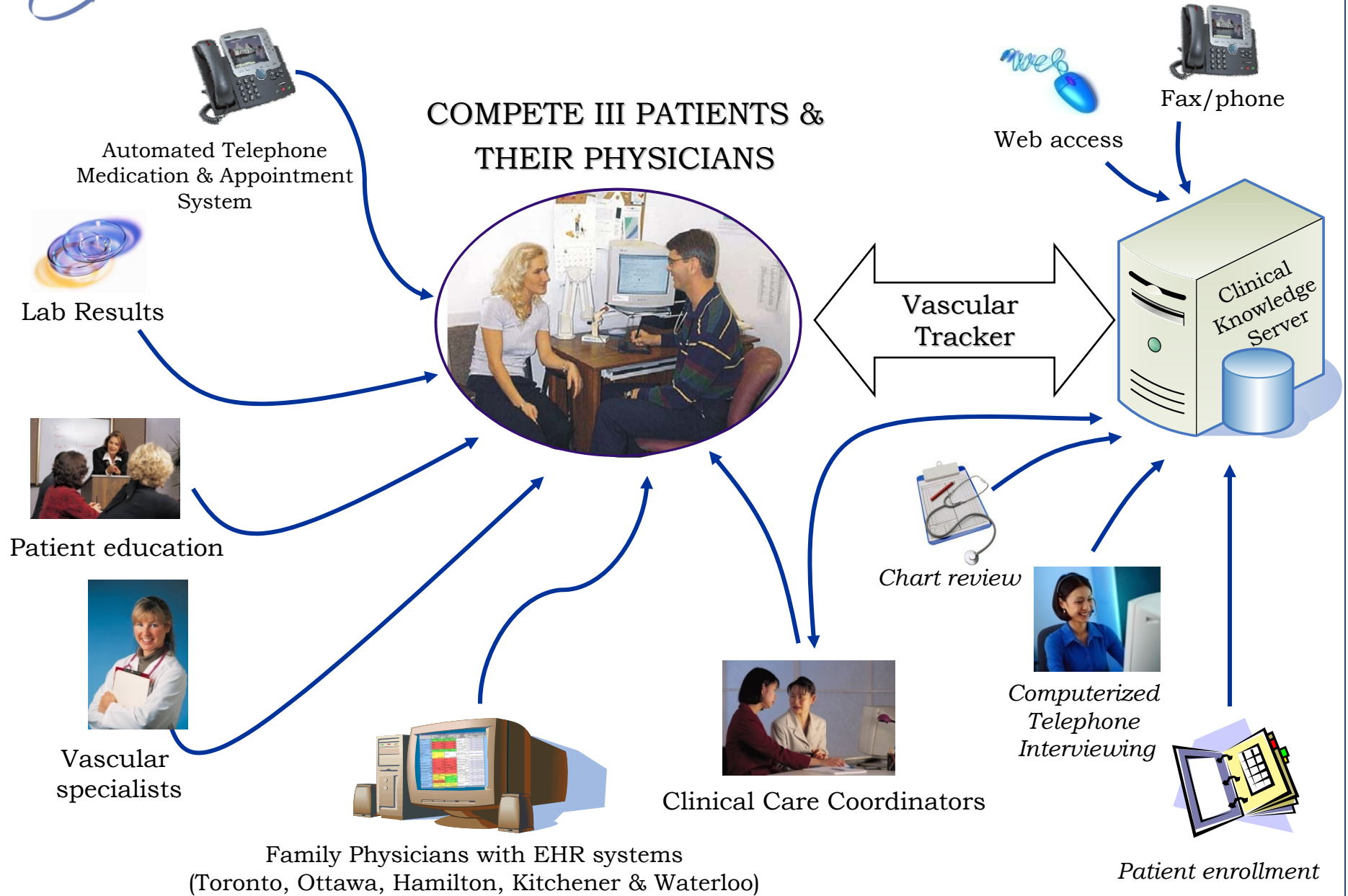
My Current Status Is...		Reset	What If My Status Were...	Calc
Gender	M		Gender <input checked="" type="radio"/> M <input type="radio"/> F	
Age (years)	57		Age (years) <input type="text" value="47"/>	
Total cholesterol	5.83		Total cholesterol <input type="text" value="5.83"/>	
HDL cholesterol	1.44		HDL cholesterol <input type="text" value="1.44"/>	
Smoker (in past month)	N		Smoker (in past month) <input type="radio"/> Y <input checked="" type="radio"/> N	
Systolic blood pressure	142		Systolic blood pressure <input type="text" value="142"/>	
Blood pressure is treated	Y		Blood pressure is treated <input checked="" type="radio"/> Y <input type="radio"/> N	
Risk of a cardiovascular event in next 10 years*	12%		Risk of a cardiovascular event in next 10 years* <input type="text" value="6%"/>	

Internet 100%



COMPETE III TRIAL OVERVIEW

COMPETE III PATIENTS & THEIR PHYSICIANS



Integrated System: Multiple Data Sources

- ✓ Paper Charts
- ✓ Web Forms
- ✓ Computer-assisted interviewing
- ✓ Fax Forms
- ✓ EMR's
- ✓ Clinical Care Coordinators
- ✓ Physicians
- ✓ Patients
- ✓ Automated Telephone Response System -Tagge

Issue #1:

Randomization Process

- Patient was the unit of randomization
- Randomization was stratified by physician
- Benefits
 - Every physician received the tracker software
- Potential challenge
 - Clustering effect/contamination
 - Analysis of CII data shows substantial clustering effect

Issue #2: Choice of Primary Outcome

- Process vs clinical outcome
 - Management is about process of care
 - Good care leads to attainment of desired clinical outcomes
- Uses process composite outcome/score
 - Dealing with challenges of composite outcomes
 - Weighting for components – done by target frequency for each
 - Still requires validation – Part of PhD student project (Ivan)

Desired Properties of Primary Outcomes

(Thabane et al. Posing the research question – not so simple. CJA 2008; in press)

- be *appropriate* (to the objectives of the study);
- be *objective* (i.e. should require less subjective judgment to measure);
- be *valid* (i.e. measures what it is intended for);
- be *reproducible/precise/reliable* (i.e. can be easily reproduced in different times/settings);
- be *clinically available* (i.e. should be available as part of clinical care);
- be *easily quantifiable* (i.e. should be easily measured);

Desired Properties of Primary Outcomes

(Thabane et al. Posing the research question – not so simple. CJA 2008; in press)

- be *efficient* (i.e. affordable to measure in terms of time and cost);
- be *sensitive* (i.e. correctly indicates presence of disease or condition of interest);
- be *specific* (i.e. correctly indicates absence of disease or condition of interest);
- be *responsive* (i.e. sensitive to changes in treatment).
That is, it should:
 - rapidly reflect the response to treatment; and
 - accurately reflect the response to treatment; and
- allow easy interpretation of results.

Table 1. COMPETE II Recommended Diabetes Management

Tracker Variable	Process Targets	Maximum Possible Score per Period (process outcomes)†	Clinical Targets	Maximum Possible Score per Period (clinical outcomes)*
Blood pressure	Quarterly	2	< 130/80 mmHg (both systolic & diastolic)	1
Cholesterol	Semi-annual	1	LDL < 2.6 mM	1
HbA1C	Semi-annual	1	< 0.07	1
Feet check	Semi-annual	1	No foot ulcers or neuropathy	1
Kidney	Semi-annual to annual	1	No microalbuminuria	1
Weight	Quarterly	2	BMI < 27	1
Physical activity	Quarterly &	1	At least 210 minutes weekly	1
Smoking	Quarterly if smoking&	1	Non-smoking	1
Eye check	Annual	N/A‡	No retinopathy	N/A‡
ASA or Equivalent	Semi-annual	N/A‡	80-325mg/day	N/A‡
ACE inhibitors	Semi-annual	N/A‡	Taking an ACEi or ARB	N/A‡
Flu shot	Annual	N/A‡	Annual dose during fall	N/A‡

† Maximum possible total composite score for process = 10 (8 variables)

* Maximum possible total composite score for clinical targets = 8 (8 variables)

‡ N/A - not used for the composite score

& Variable recommended target was quarterly, but data only available once pre and post.

Issue #3:

Data Collection

- Balancing the research needs vs uninterrupted patient care
 - ✓ Pragmatism was a key factor in assessing effect of EMR in the real-world
- Primary sources
 - ✓ Chart Review – with a random sample done in duplicate to assess reliability
 - ✓ CDR (clinical data repository)
 - ✓ Med CDR – for medications
- Secondary sources – CATI/SPSS

Issue # 4:

Analysis and sample size

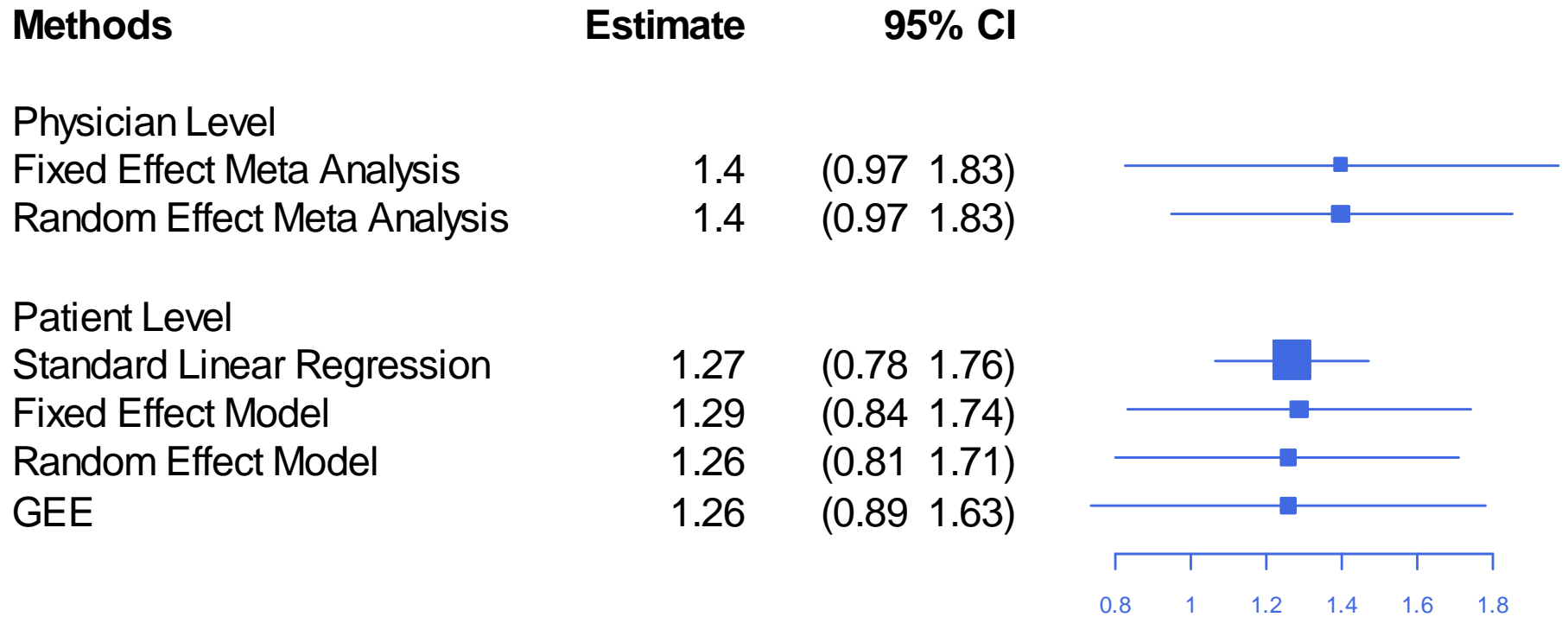
- Unit of randomization: Patient
- Unit of analysis/inference:
 - Patient or physician
- Method of analysis: several options
 - Patient or physician level
 - Accounting for potential clustering
 - Accounting for stratification

Results

Level of Analysis	Method of Analysis	Effect Est	SE	95% CI	P-value
Physician	Fixed Effect Meta Analysis	1.40	0.30	(0.97 1.83)	<0.0001
	Random Effect Meta analysis	1.40	0.30	(0.97 1.83)	<0.0001
Patient	Standard Linear Regression	1.27	0.25	(0.78 1.76)	<0.0001
	Fixed Effect Model	1.29	0.23	(0.84 1.74)	<0.0001
	Random Effect Model	1.26	0.23	(0.81 1.71)	<0.0001
	GEE	1.26	0.19	(0.89 1.63)	<0.0001

ICC estimate: 0.124

Results



Which Method to use

- Need for simulation studies to compare the efficiency of
 - Composite score vs multivariate/multiple outcomes
 - Different methods to adjust for both stratification and clustering

Concluding Remarks

- Managing chronic diseases in practice is a challenge
- Operationalizing management guidelines in practice requires pragmatism
- Evaluation of effect/impact requires careful planning
- There are some design and analysis challenges to deal with

Acknowledgements

- COMPETE II & III Teams
- Jinhui Ma and Rachel Chu