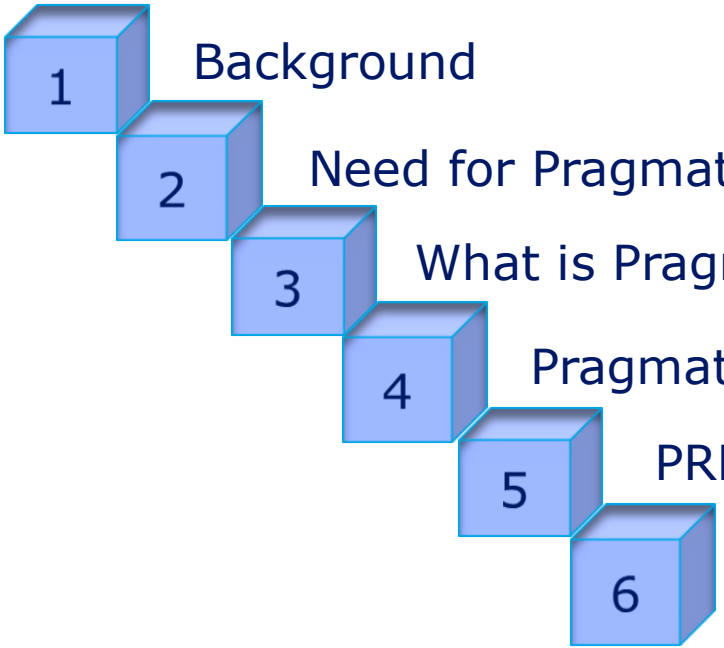
Pragmatic Clinical Trials – A Vehicle to Explore Real World Evidence

Sohan Dey
Senior Statistician
Biostatistics & Programming
Novo Nordisk Service Centre India Private Ltd.

Disclaimer

THE VIEWS AND OPINIONS EXPRESSED IN THIS PRESENTATION ARE THOSE OF THE AUTHOR AND DO NOT NECESSARILY REPRESENT OFFICIAL POLICY OR VIEWS OF NOVO NORDISK

Agenda



Background

Need for Pragmatic clinical trials

What is Pragmatic clinical trial?

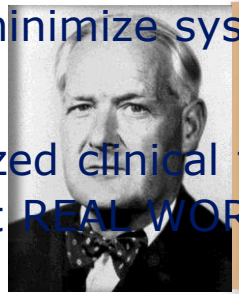
Pragmatic-Explanatory Continuum

PRECIS

Example

Background

- Traditional randomized clinical trials study designs help in providing the decisions about the effect of
  - different interventions
  - minimize systematic errors by randomization, blinding, allocation etc.



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one

- Randomized clinical trials take place in restricted conditions that do not represent REAL WORLD clinical practice.
- Often trials are EXPLANATORY or MECHANISTIC in that their main aim is to focus more on the efficacy evaluation of drug therapies but rarely produce findings that are easily put into practice.

Background

Major challenges related to traditional clinical research

- Participants are often selected on the basis of strict clinical criteria and the selected group is homogenous
- Participants have only the target condition and are subject to strict dosing conditions and monitoring

> "If we want more evidence-based practice, we need more practice-based evidence."
>
> *L. W. Green, American Journal of Public Health*, 2006.

Need for Pragmatic Clinical Trials

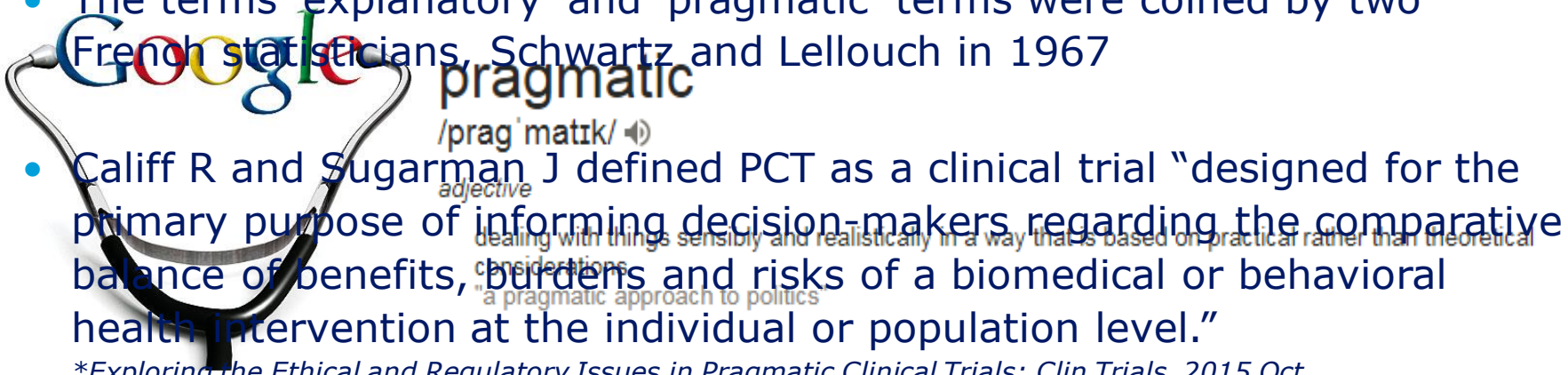
- Despite the fact of many RCTs being conducted every year, the systematic reviews state that results of RCTs still lack enough evidence to support the clinical decisions.

- There is an increasing expression of doubt as to whether the plethora of available evidence and ongoing data are translatable and usable in real life.

- Need trials designed to answer questions to support treatment and policy decision-making and producing widely applicable results rather than to only evaluate a therapy’s biological effects.

What is Pragmatic Clinical Trial (PCT)?

- The terms ‘explanatory’ and ‘pragmatic’ terms were coined by two French statisticians, Schwartz and Lellouch in 1967



- Califf R and Sugarman J defined PCT as a clinical trial “designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level.”

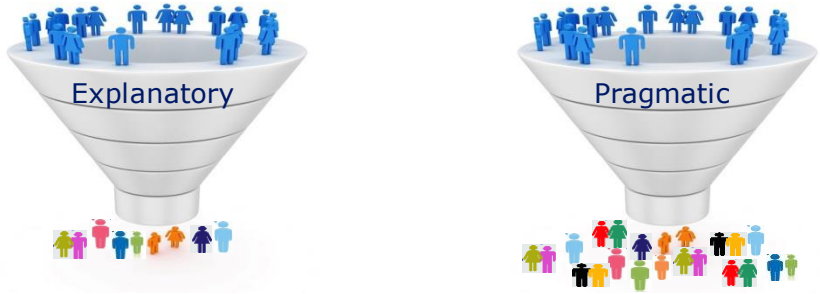
**Exploring the Ethical and Regulatory Issues in Pragmatic Clinical Trials; Clin Trials, 2015 Oct*

- PCTs may provide the opportunity to generate evidence in an earlier stage than in the current development paradigm where real-world evidence generally is only collected post-launch.

What is Pragmatic Clinical Trial (PCT)?

- Real World Evidence focused methodology

- The design of pragmatic trials mimic as closely as possible ROUTINE clinical practice in terms of
  - study population
  - interventions
  - comparators
  - outcomes



- Focus on collecting clinical evidence on the comparative effects of treatments that are relevant to patients, caregivers, and therapeutic decision making.

Characteristics of PCT

- Interventions may be medical, behavioral or technical and may be measured in patients, clinicians or across healthcare systems.
- PCTs rely on patient heterogeneity to maximize generalizability to real-world care and minimal exclusion criteria are used.
- PCTs typically are large-scale studies and require streamlined research operations.
- PCTs can inform policy makers and health care providers of a treatment's cost in real-life situations
- Endpoints encompass a broad array of health outcomes, health behaviors and economic impacts.

Explanatory vs. Pragmatic

Design	Explanatory	Pragmatic
Validity	Strongly internal	Strongly external
Study Population	Homogeneous	Heterogeneous
Study Sites	Clinical Research/Academic	Real-World Medical Practice
Endpoints	Symptoms; biomarkers	Health/ behavioural/ economic outcomes
Follow-up	Longer-term follow-up times	Short-term follow-up time

The Explanatory-Pragmatic Continuum

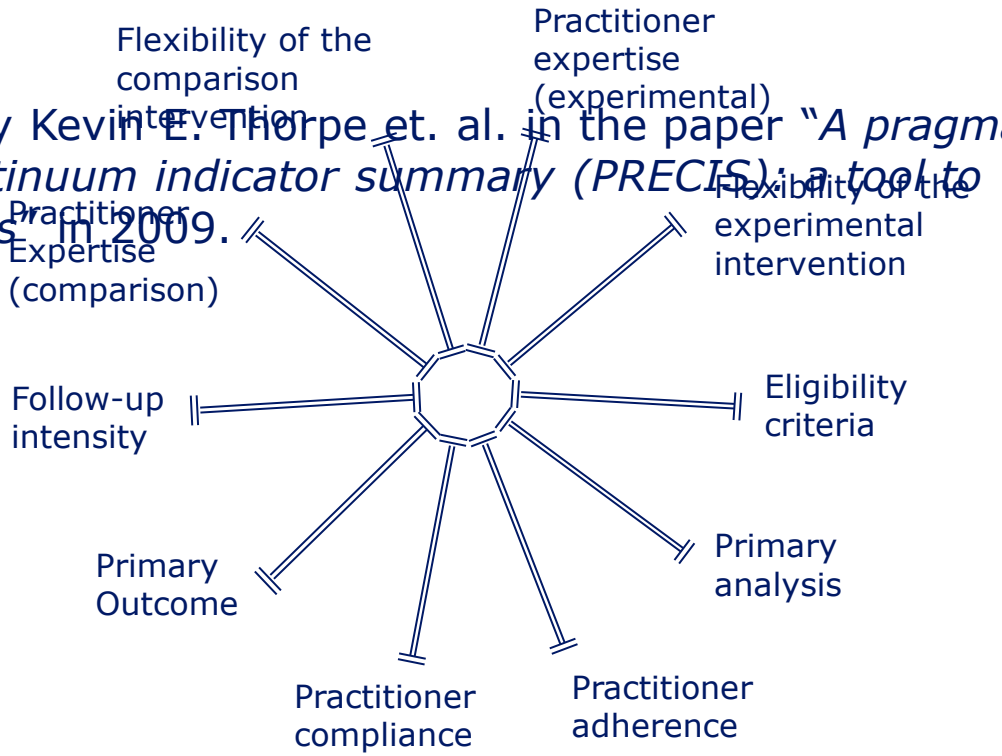
- PCT's don't take away from basic science or diminish the importance of traditional clinical trials — a balance is needed.
- It is important to recognize the limitations of such a dichotomous approach because most trials contain components of both approaches.
- Explanatory clinical trials and Pragmatic clinical trials exist on a continuum

Explanatory Trial
Can an intervention work under ideal conditions?

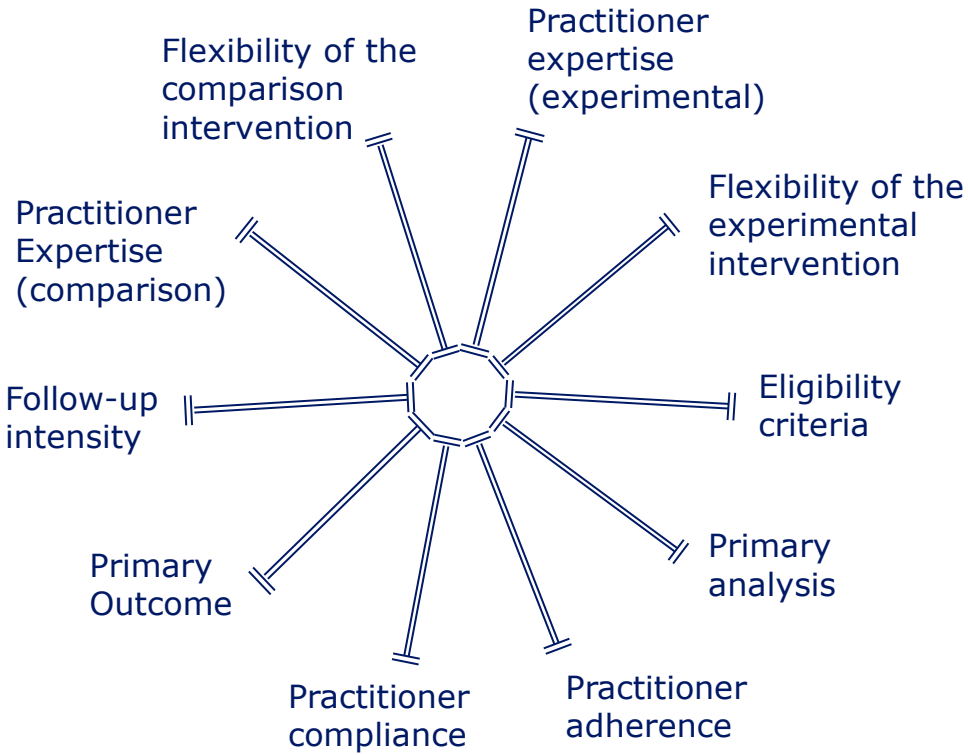
Pragmatic Trial
We now know it can work, but how well does it work in real world clinical practice?

PRagmatic-Explanatory Continuum Indicator Summary (PRECIS)

First introduced by Kevin E. Thorpe et. al. in the paper "*A pragmatic - explanatory continuum indicator summary (PRECIS): a tool to help trial designers*" in 2009.



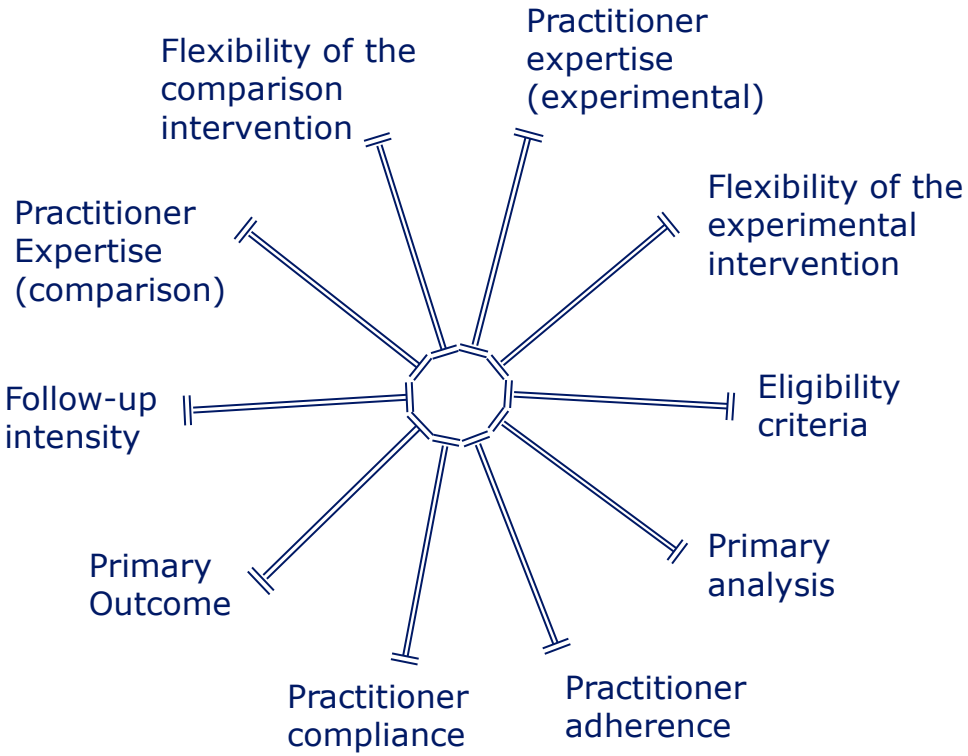
PRagmatic-Explanatory Continuum Indicator Summary (PRECIS)



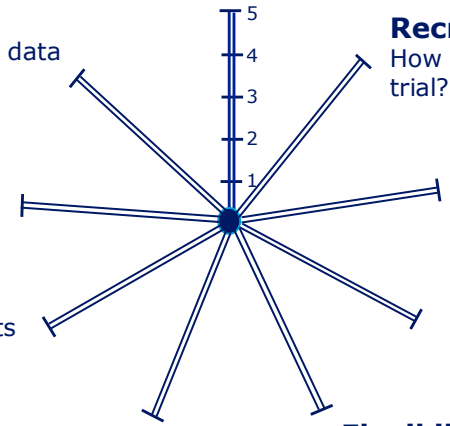
PRagmatic-Explanatory Continuum Indicator Summary (PRECIS)

Weaknesses:

- no rating scale
- problems with some domains
- needed better guidance
- not validated



PRECIS-2 Wheel



Eligibility
Who is selected to participated in the trial?

Recruitment
How are participants recruited in the trial?

Setting
Where is the trial being done?

Organization
What expertise and resources are needed to deliver the intervention?

Flexibility: delivery
How should the intervention be delivered?

Flexibility: adherence
What measures are in place to ensure participants adhere to the intervention?

Follow-up
How closely are participants followed-up?

Primary outcome
How relevant is it to participants?

Primary Analysis
To what extent are all data included?

1 - Very explanatory

2 – Rather explanatory

3 – Equally pragmatic and explanatory

4 – Rather pragmatic

5 – Very pragmatic

A toolkit with guidance and practical help is available to download from www.precis-2.org

**Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M.*

PRECIS-2 Domains

Domain	1- Very Explanatory	5 - Very Pragmatic
Eligibility	Lots of exclusions Uses many selection tests not used in usual care.	Essentially identical to usual care
Recruitment	Targeted invitation letters, advertising in newspapers, radio plus incentives and other routes	Recruitment through usual appointments or clinic
Setting	Only a single center, or specialized trial/academic centers	Identical settings to usual care
Organization	Additional staff training, require more than usual experience or certification and additional resources	Uses identical organization to usual care

**Use of PRECIS-2 Ratings in the NIH Health Care Systems Research Collaboratory,* Presented by Karin Johnson and Gila Neta

PRECIS-2 Domains

Domain	1- Very Explanatory	5 - Very Pragmatic
Flexibility (delivery)	Strict protocol, monitoring and measures to improve compliance, with specific advice on allowed co-interventions and complications	Identical flexibility to usual care
Flexibility (adherence)	Exclusion based on adherence, and measures to improve adherence if found wanting	No more than usual encouragement to adhere to the intervention
Follow-up	More frequent, longer visits, unscheduled visits triggered by primary outcome event or intervening event, and more extensive data collection	No more than usual follow up

**Use of PRECIS-2 Ratings in the NIH Health Care Systems Research Collaboratory,* Presented by Karin Johnson and Gila Neta

PRECIS-2 Domains

Domain	1- Very Explanatory	5 - Very Pragmatic
Primary Outcome	Surrogate, physiological outcome Central adjudication or assessment expertise that is not available in usual care. Measured earlier than in usual care	Outcome of obvious importance to participants
Primary Analysis	Excludes ineligible post-randomization participants, includes only completers or those following the treatment protocol	Intent to treat with all available data

**Use of PRECIS-2 Ratings in the NIH Health Care Systems Research Collaboratory,* Presented by Karin Johnson and Gila Neta

Example

The DIrect Statin COmparison of LDL-C Values: an Evaluation of Rosuvastatin therapY (DISCOVERY)

**Achieving lipid goals in real life: the Dutch DISCOVERY Study : A. F. E. Bots, J. J. P. Kastelein*

Design:

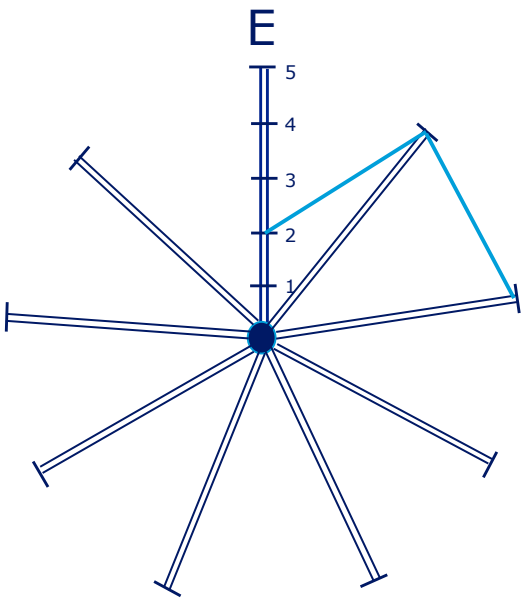
An open-label, 12-week multi-center, randomized, 4-arm, parallel-group study conducted in 152 primary care physician practices in the Netherlands with an allocation ratio of 3:1:1:1.

The trial was designed to compare the effects of rosuvastatin with those of atorvastatin, simvastatin or pravastatin on low-density lipoprotein cholesterol (LDL-C) goal achievement in a primary care setting.

Primary Outcome:

The percentage of patients achieving European LDL-C goal (<3.0 mmol/l) at week 12

Example



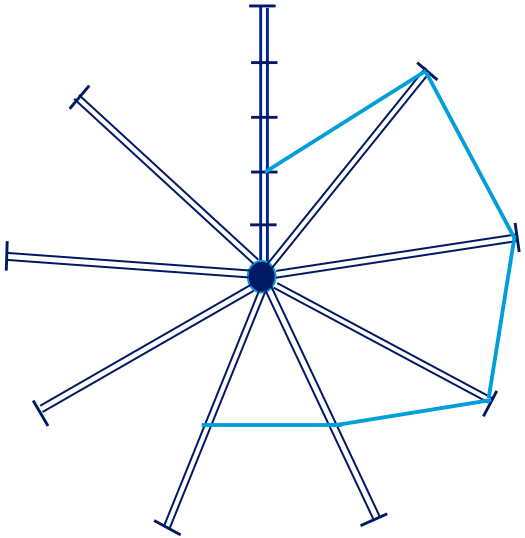
Eligibility
Men and women (aged ≥18 years) with
a. type IIa or IIb primary hypercholesterolemia
b. a 10-year CV risk >20% or a history of CHD or other established atherosclerotic disease
c. fasting triglycerides (TG) ≤4.52 mmol/L at visit 2 (week 0)

Score: 2

Recruitment
Subjects were selected by cardiologists, internists, and general practitioners (when needed if previously consulted by cardiologist) from a primary or secondary prevention subject population.
Score: 5

Setting
Conducted in 152 primary care physician practices in the Netherlands
Score: 5

Example

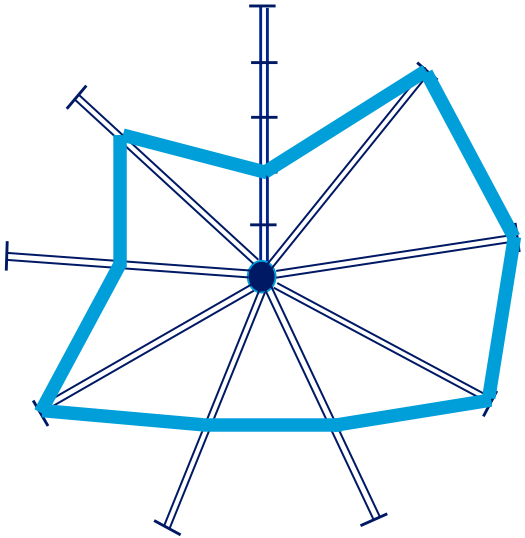


Organization
The trial was conducted in accordance with the ethical principles in the Declaration of Helsinki, ICH GCP guidelines and local regulatory requirements
Score: 5

Flexibility (delivery)
Statin-naive patients underwent 6 weeks of dietary counseling, dose titration might have been required in high-risk patients to enable a greater proportion to achieve more stringent goals.
Score: 3

Flexibility (adherence)
Tolerability was monitored for the 12-week study
Score: 3

Example



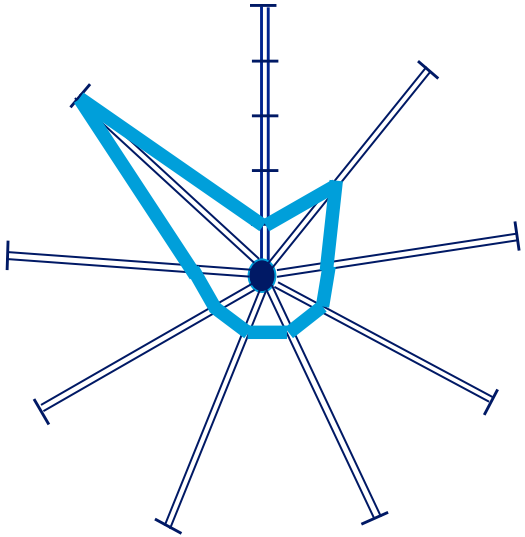
Follow-up
Similar to usual care setting with blood samples being drawn only at screening (week −2), randomization (week 0), week 12
Score: 5

Primary outcome
Primary endpoint was the percentage of patients achieving 1998 European LDL-C goal (<3.0 mmol/l) at week 12
Score: 3

Primary analyses
Intention-to-treat but also post-hoc analyses
Score: 4

Example

Epidemiological study on post-prandial anti-inflammatory and antioxidant effects of extra virgin olive oil.
The aim of this study was to evaluate changes in inflammatory and oxidative stress markers.
Intervention Drug - 50mg Extra virgin olive oil together with 150g of potatoes



Conclusion

- Pragmatic clinical trials ensures that the outcomes used to assess effectiveness are valid and easily understood by a range of users.
- Estimates of treatment effect in pragmatic clinical trials should be directly generalizable to clinical practice and relevant to patients and decision making in real-world clinical practice.
- The majority of clinical trials are neither entirely pragmatic nor entirely explanatory—they are part of a continuum.
- PRECIS-2 tool is one method for assessing where on the pragmatic–explanatory continuum a trial resides.
- PRECIS-2 tool is more to help trialists think about the impact of their design decisions would have on applicability in the Real World.

References

- *Robert M Califf, Jeremy Sugarman- Exploring the Ethical and Regulatory Issues in Pragmatic Clinical Trials; Clin Trials, 2015 Oct*
- *Mark J Cziraky, Kay M. Larholt, Michael Pollock- Conducting Pragmatic Trials: Design and Infrastructure Considerations for Successful Implementation of Trials Based on Real-World Evidence*
- *Use of PRECIS-2 Ratings in the NIH Health Care Systems Research Collaboratory; Presented by Karin Johnson and Gila Neta*
- *Impact of a community health worker HIV treatment and prevention intervention in an HIV hotspot fishing community in Rakai, Uganda (mLAKE): study protocol for a randomized controlled trial: Larry W. Chang, Ismail Mbabali, Xiangrong Kong, Heidi Hutton, K. Rivet Amico, Caitlin E. Kennedy, Fred Nalugoda, David Serwadda, Robert C. Bollinger, Thomas C. Quinn, Steven J. Reynolds, Ronald Gray, Maria Wawer, Gertrude Nakigoz*
- *Achieving lipid goals in real life: the Dutch DISCOVERY Study : A. F. E. Bots, J. J. P. Kastelein*
- *www.precis-2.org*

THANK YOU

Contact: SODX@NOVONORDISK.COM


QUESTIONS?