Get Real

Real-Life Data in Drug Development

Identifying and addressing the Operational Challenges of Pragmatic Trials

GetReal work package 3

October 6, 2016

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The why and how of pragmatic trials

Rick Grobbee

Julius Center, UMCU, the Netherlands

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Why is there a need for Real World Evidence?

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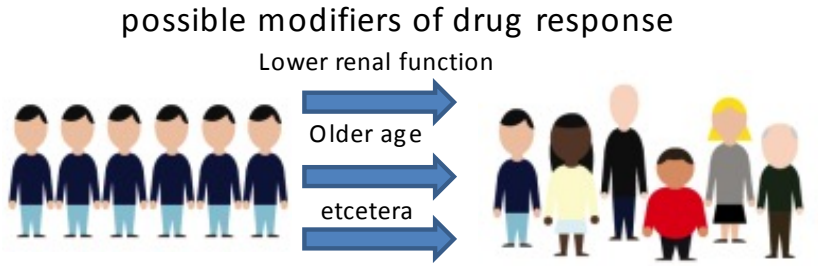
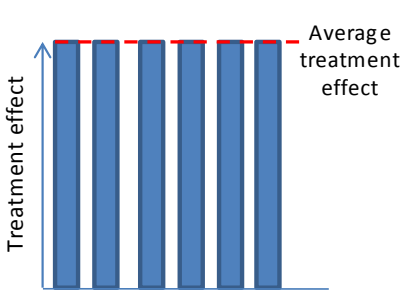
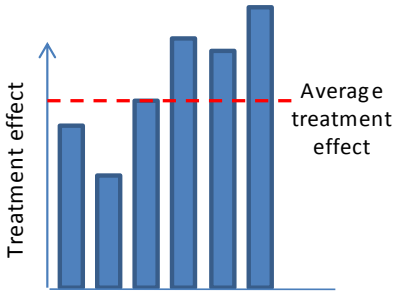
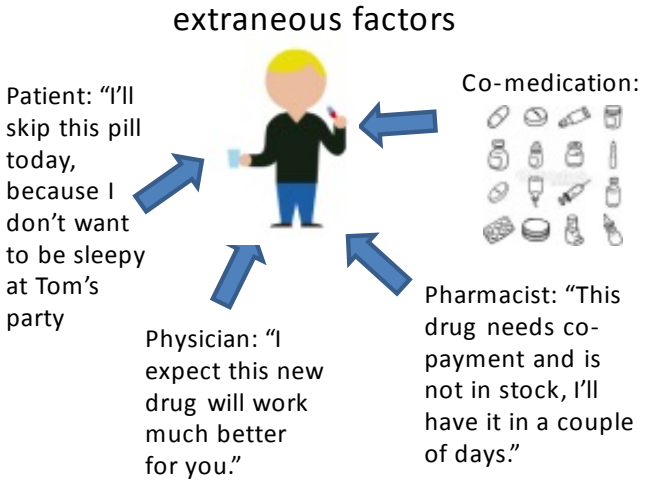
Generalizability of study results to patient population of interest

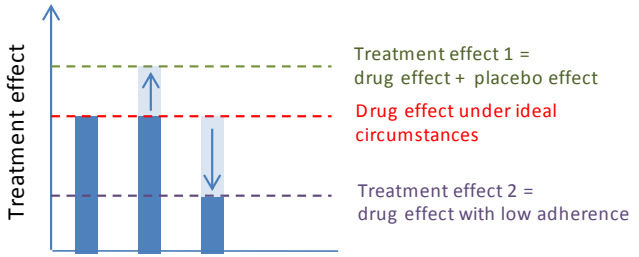






Drug vs treatment strategy





Zuidgeest et al., submitted

Where do pragmatic trials fit in?

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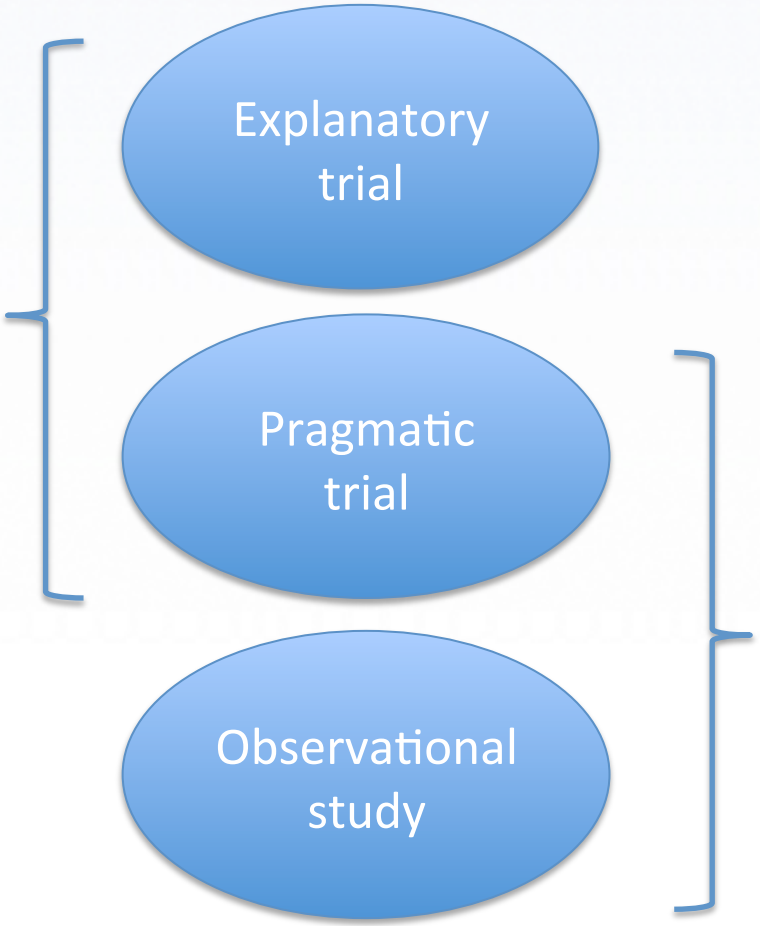
Randomization
=
no prognostic incomparability between patient groups



Real World Evidence
=
How does treatment strategy A compare to treatment strategy B (often usual care) in daily clinical practice?

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What are pragmatic trials?

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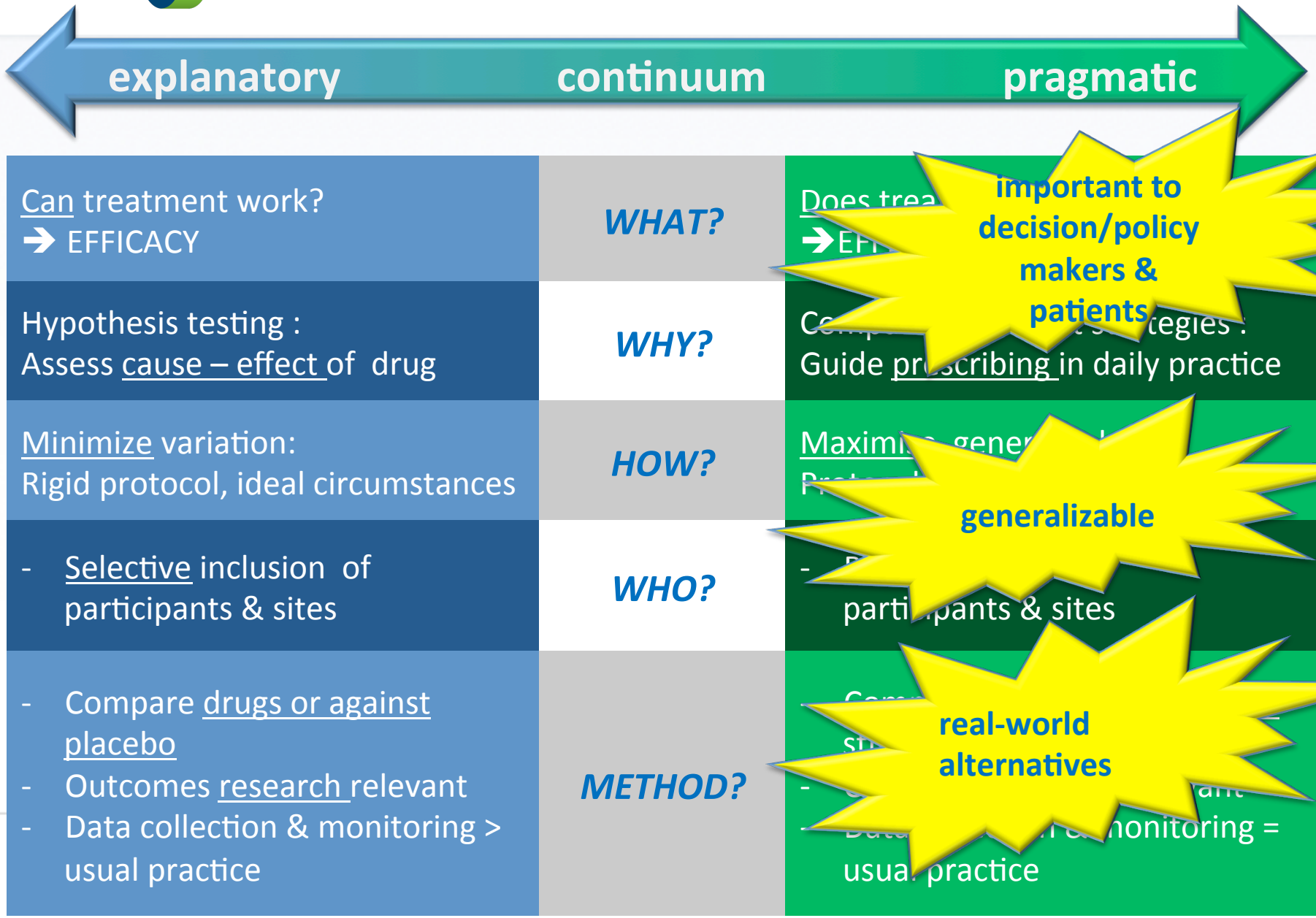

Pragmatic trials on the rise

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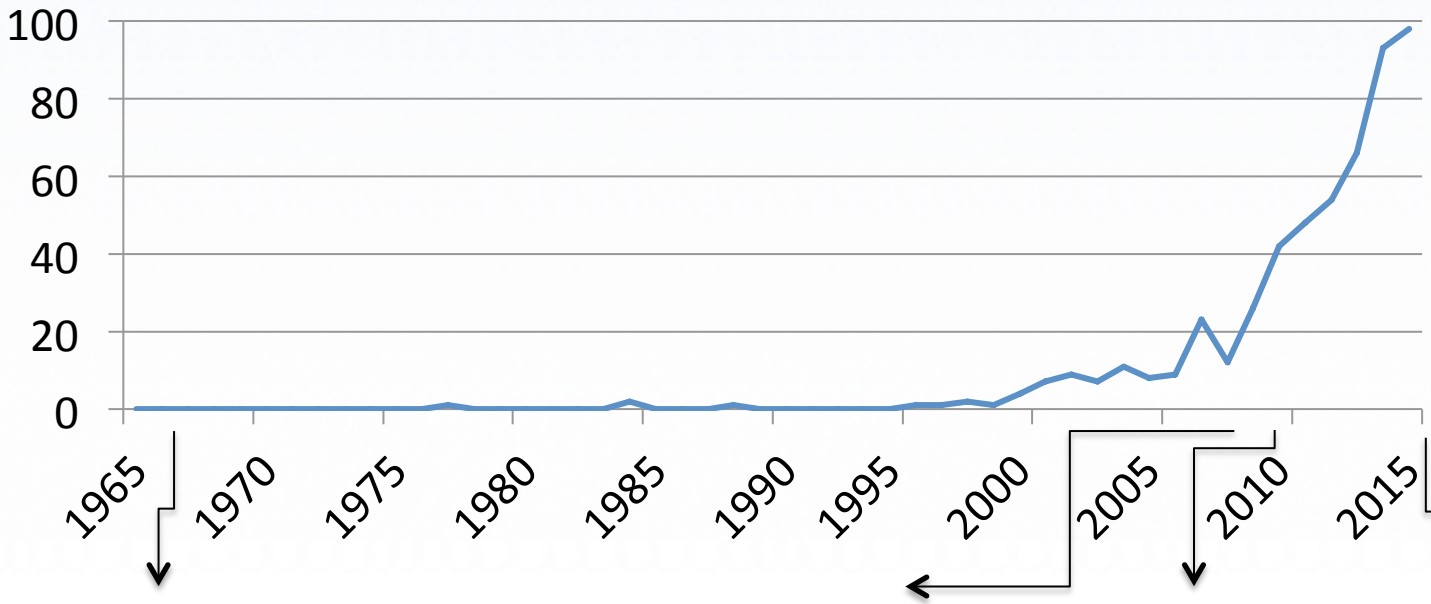
Number of pragmatic trials*



*Based on pubmed search per year on article type "Clinical Trial" with" both the words "pragmatic" and "trial" in the title

pragmatic[ti] AND trial[ti] AND ((Clinical Trial[ptyp] OR Pragmatic Clinical Trial[ptyp]) AND ("jjjj/01/01"[PDAT] : "jjjj/12/31"[PDAT]))

1967
Term "Pragmatic trial" introduced
Schwartz&Lellouch Journal of Chronic Diseases 1967

2008
Extension consort statement
Zwarenstein BMJ 2008

2009
PRECIS tool

Thorpe JCE 2009

2015
Update to PRECIS-2 tool
Loudon BMJ 2015

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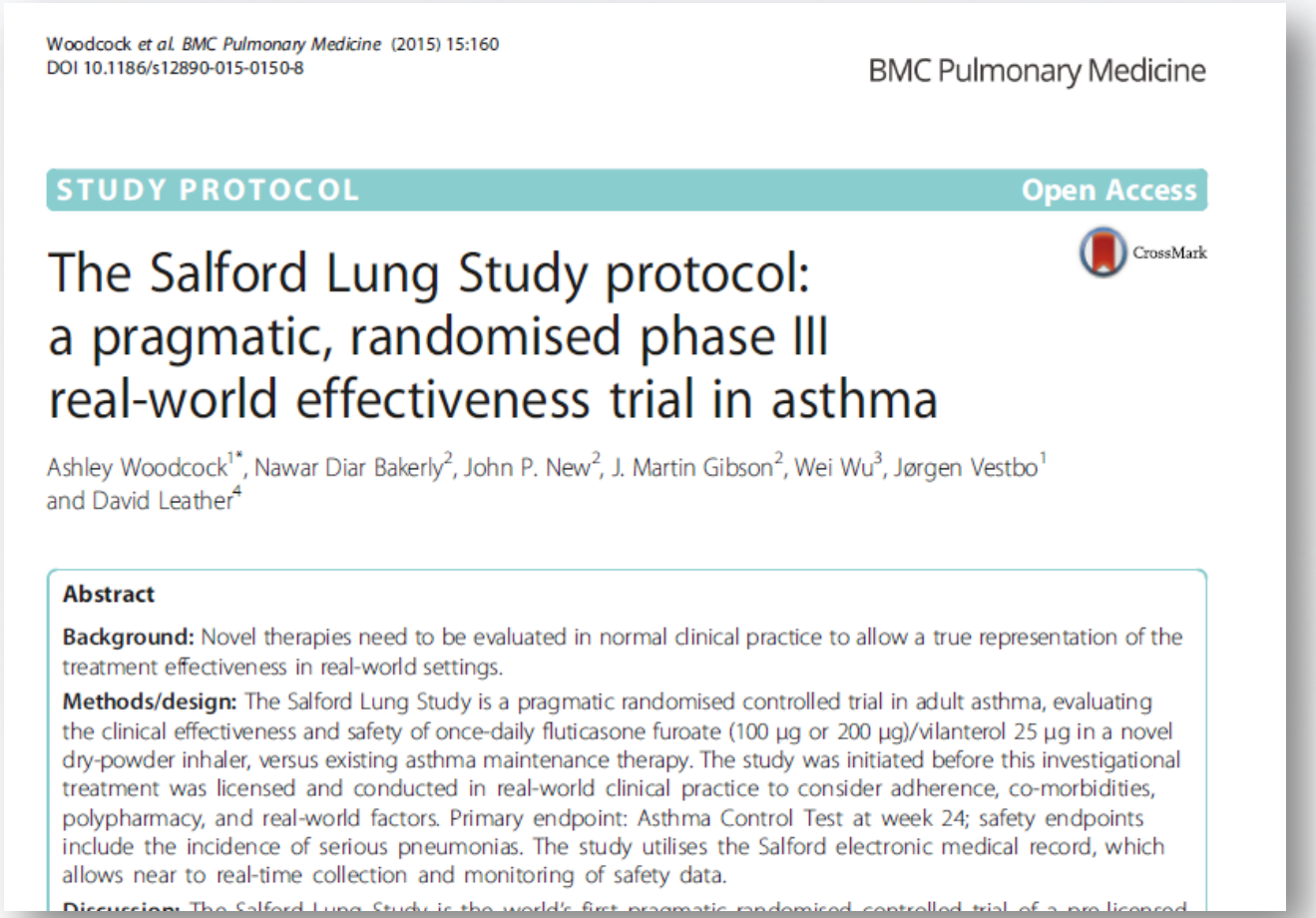
Pragmatic trial example 1



Woodcock *et al. BMC Pulmonary Medicine* (2015) 15:160
DOI 10.1186/s12890-015-0150-8

BMC Pulmonary Medicine

STUDY PROTOCOL Open Access

The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in asthma

Ashley Woodcock[1*], Nawar Diar Bakerly[2], John P. New[2], J. Martin Gibson[2], Wei Wu[3], Jørgen Vestbo[1] and David Leather[4]

Abstract

Background: Novel therapies need to be evaluated in normal clinical practice to allow a true representation of the treatment effectiveness in real-world settings.

Methods/design: The Salford Lung Study is a pragmatic randomised controlled trial in adult asthma, evaluating the clinical effectiveness and safety of once-daily fluticasone furoate (100 μg or 200 μg)/vilanterol 25 μg in a novel dry-powder inhaler, versus existing asthma maintenance therapy. The study was initiated before this investigational treatment was licensed and conducted in real-world clinical practice to consider adherence, co-morbidities, polypharmacy, and real-world factors. Primary endpoint: Asthma Control Test at week 24; safety endpoints include the incidence of serious pneumonias. The study utilises the Salford electronic medical record, which allows near to real-time collection and monitoring of safety data.

Discussion: The Salford Lung Study is the world's first pragmatic randomised controlled trial of a pre-licensed

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Pragmatic trial example 1

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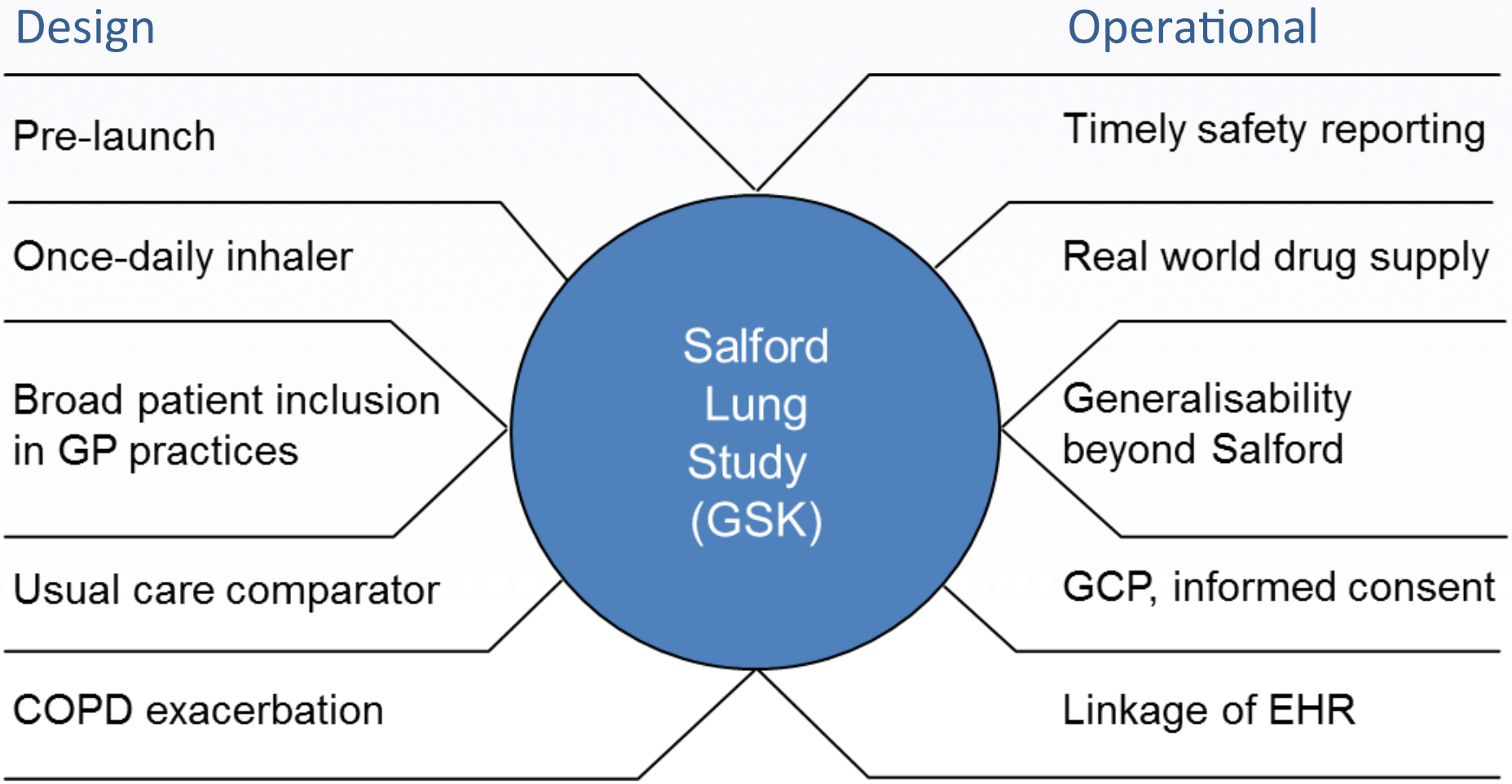

Nawar 2013; New 2014

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Pragmatic trial example 2

European Heart Journal Advance Access published October 4, 2016

European Heart Journal (2016) **0**, 1–9
doi:10.1093/eurheartj/ehw387

CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT)

Thomas M. MacDonald[1]*, Chris J. Hawkey[2], Ian Ford[3], John J.V. McMurray[4], James M. Scheiman[5], Jesper Hallas[6], Evelyn Findlay[1], Diederick E. Grobbee[7], F.D. Richard Hobbs[8], Stuart H. Ralston[9], David M. Reid[10], Matthew R. Walters[4], John Webster[10], Frank Ruschitzka[11], Sir Lewis D. Ritchie [12], Susana Perez-Gutthann[13], Eugene Connolly[4], Nicola Greenlaw[3], Adam Wilson[1], Li Wei[14], and Isla S. Mackenzie[1]

[1]Medicines Monitoring Unit (MEMO), Division of Molecular & Clinical Medicine, University of Dundee, Ninewells Hospital & Medical School Dundee, Dundee DD1 9SY, UK; [2]Faculty of Medicine & Health Sciences, University of Nottingham, Queen's Medical Centre Nottingham, Nottingham NG7 2UH, UK; [3]Robertson Centre for Biostatistics, University of Glasgow, Glasgow G12 8QQ, UK; [4]British Heart Foundation Cardiovascular Research Centre, University of Glasgow,126 University Place, GlasgowG12 8TA, UK; [5]Division of Gastroenterology, University of Michigan Medical School, 1500 E Medical Center Drive, Ann Arbor, MI 48109, USA; [6]Department of Public Health, Clinical Pharmacology, University of Southern Denmark, J. B. Winsløws Vej 19, 2.5000 Odense, Denmark; [7]Julius Center for Health Sciences and Primary Care and Julius Clinical

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Pragmatic trial example 2

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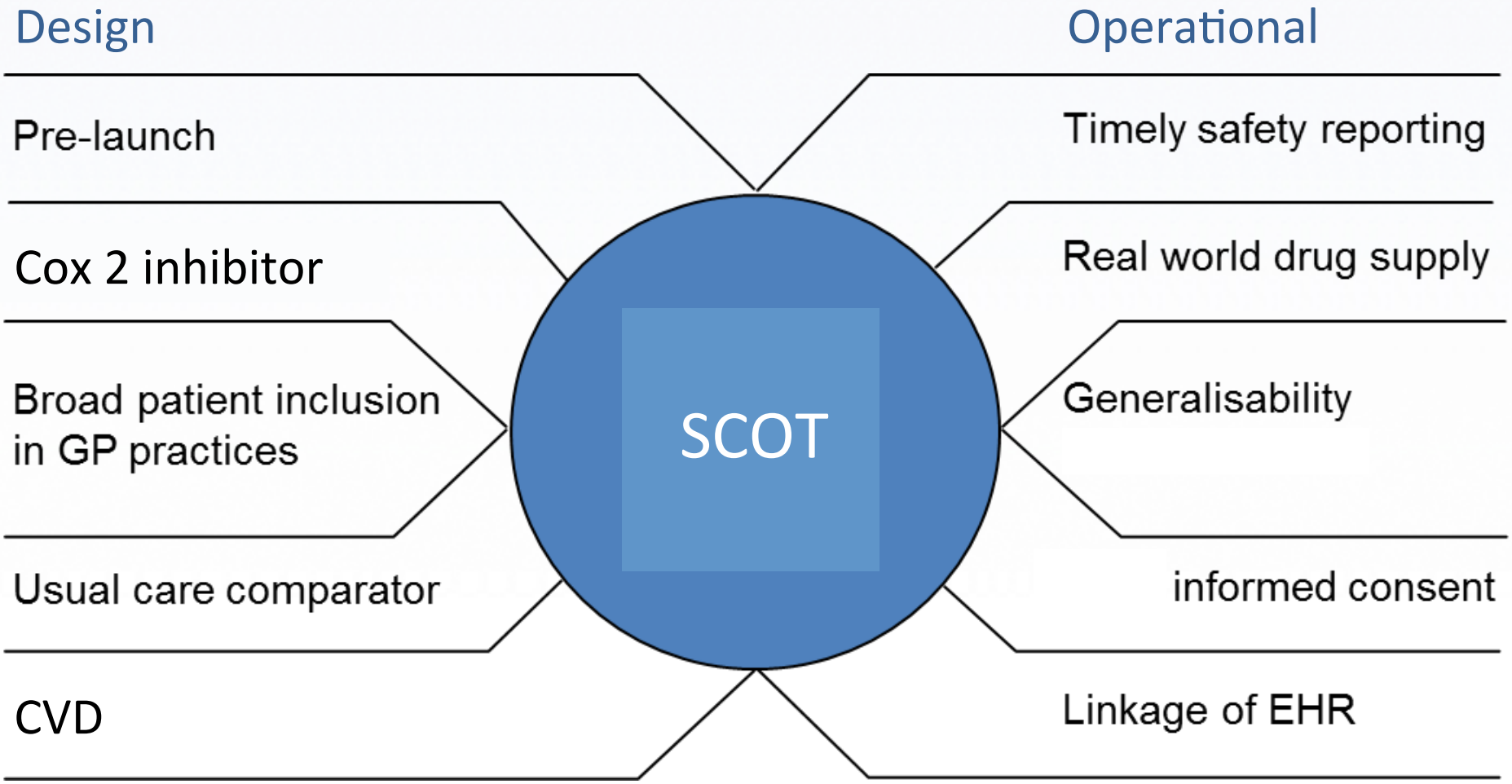

MacDonald et al. 2016

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Need for guidance and tools

- Operationalization of more pragmatic design choices not always straightforward
- Operational challenges often different than in traditional RCT and unanticipated

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A decision support tool for pragmatic trials

Mira Zuidgeest

Julius Center, UMCU, the Netherlands

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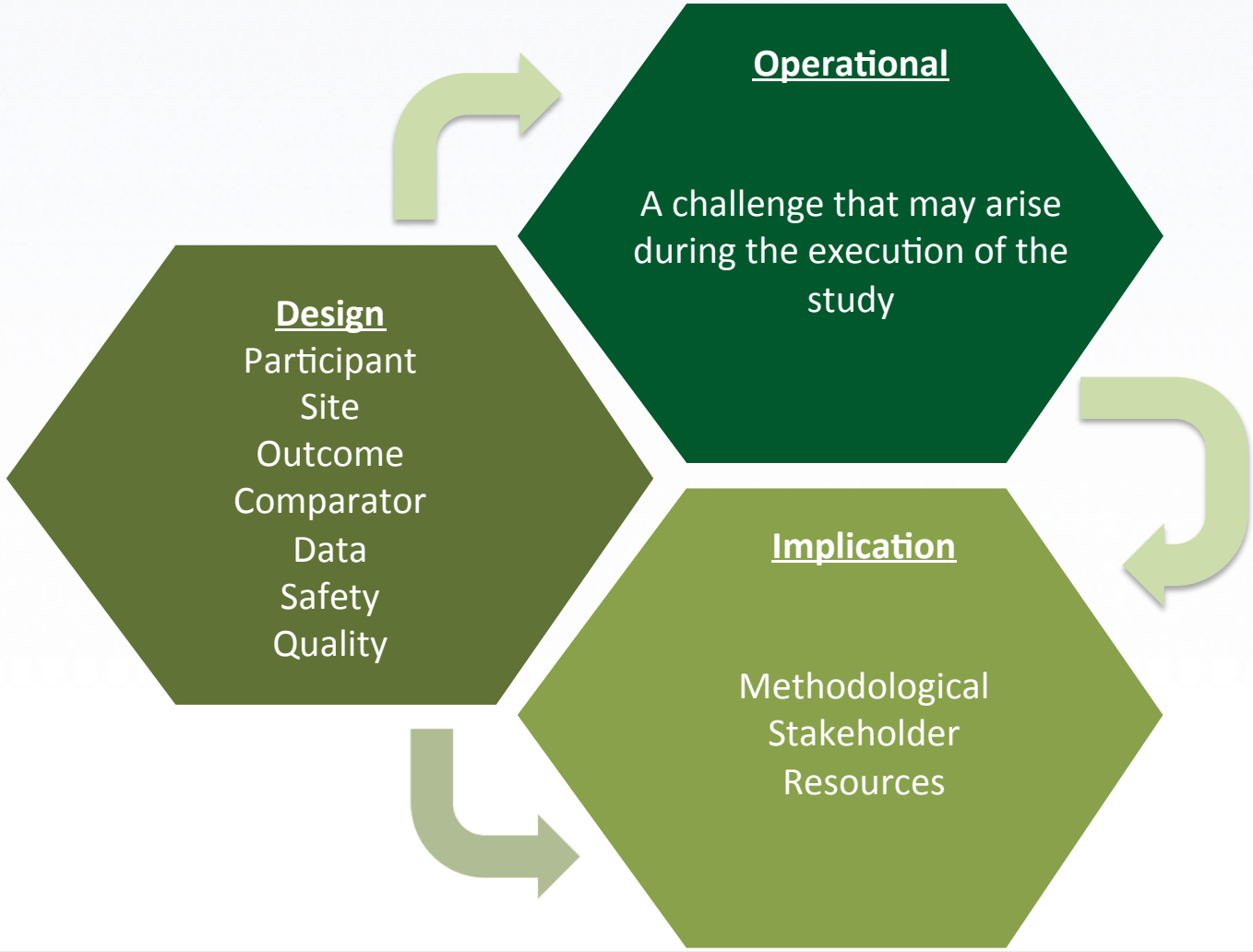
Complex interplay



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Get Real Complex interplay - example

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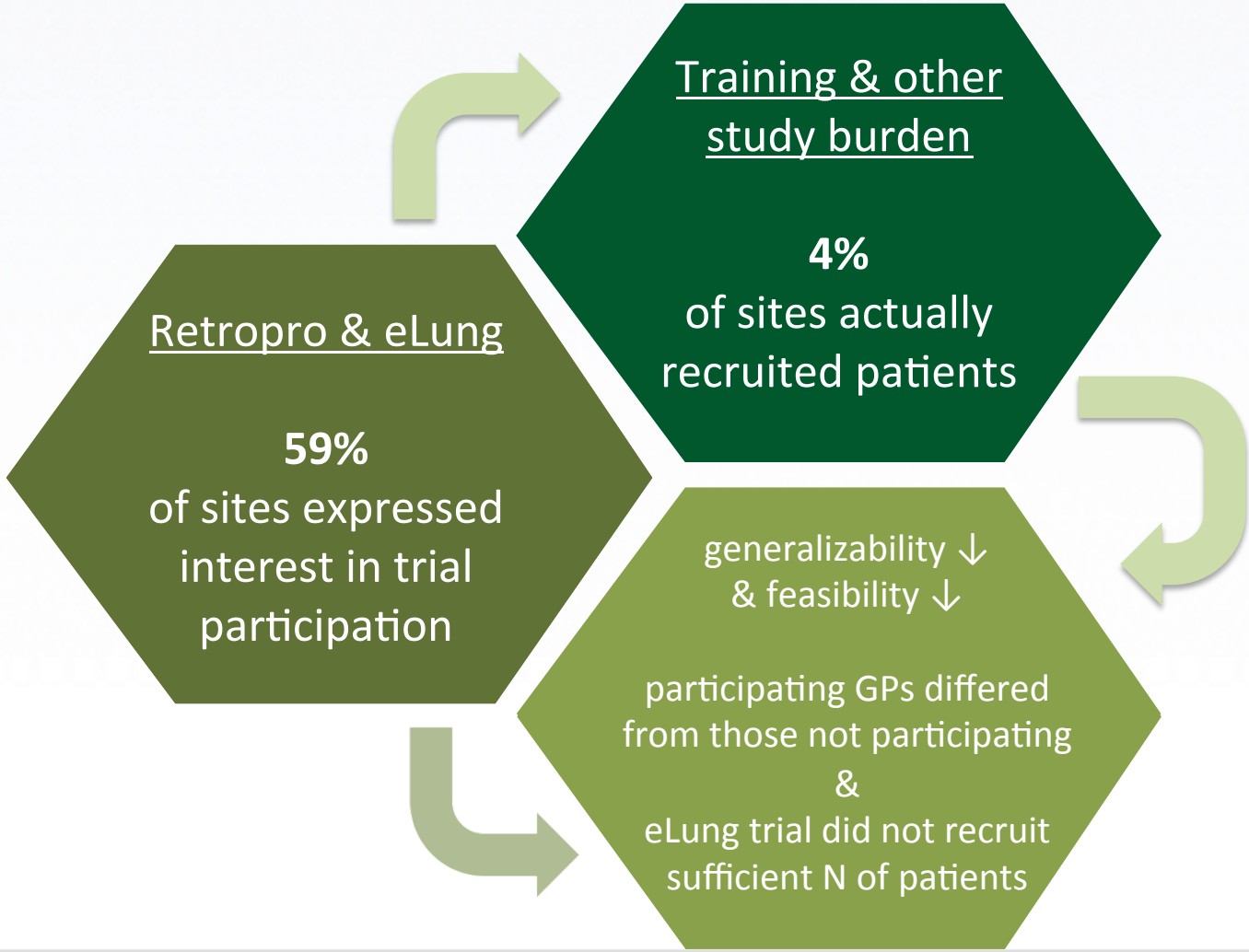

Van Staa 2014

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The goal of PragMagic

aim
- facilitate the design & planning of pragmatic trials

by
- insights: consequences of design & operational challenges
- visualize complex interplay systematically: decision support tool

to
- maximize generalizability of trial findings
- ensure validity & operational feasibility

What PragMagic is NOT

- NOT a decision-making tool;
- NOT a checklist to assure (regulatory/ethical) compliance;
- NOT a quality check/verdict on study design.

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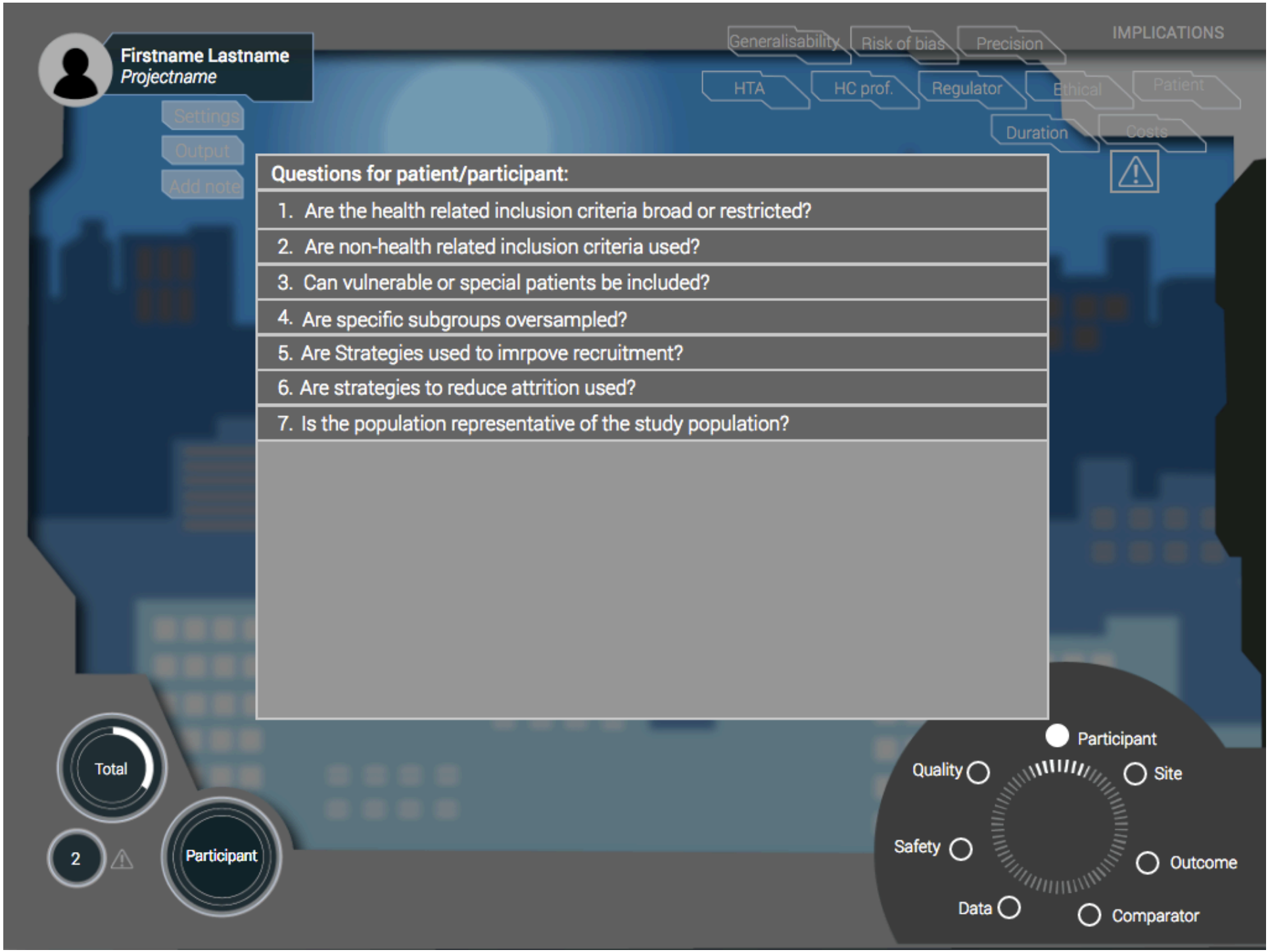
Firstname Lastname
Projectname
Settings
Output
Add note
IMPLICATIONS
Generalisability
Risk of bias
Precision
HTA
HC prof.
Regulator
Ethical
Patient
Duration
Costs
Total
2
Participant
Quality
Site
Safety
Outcome
Data
Comparator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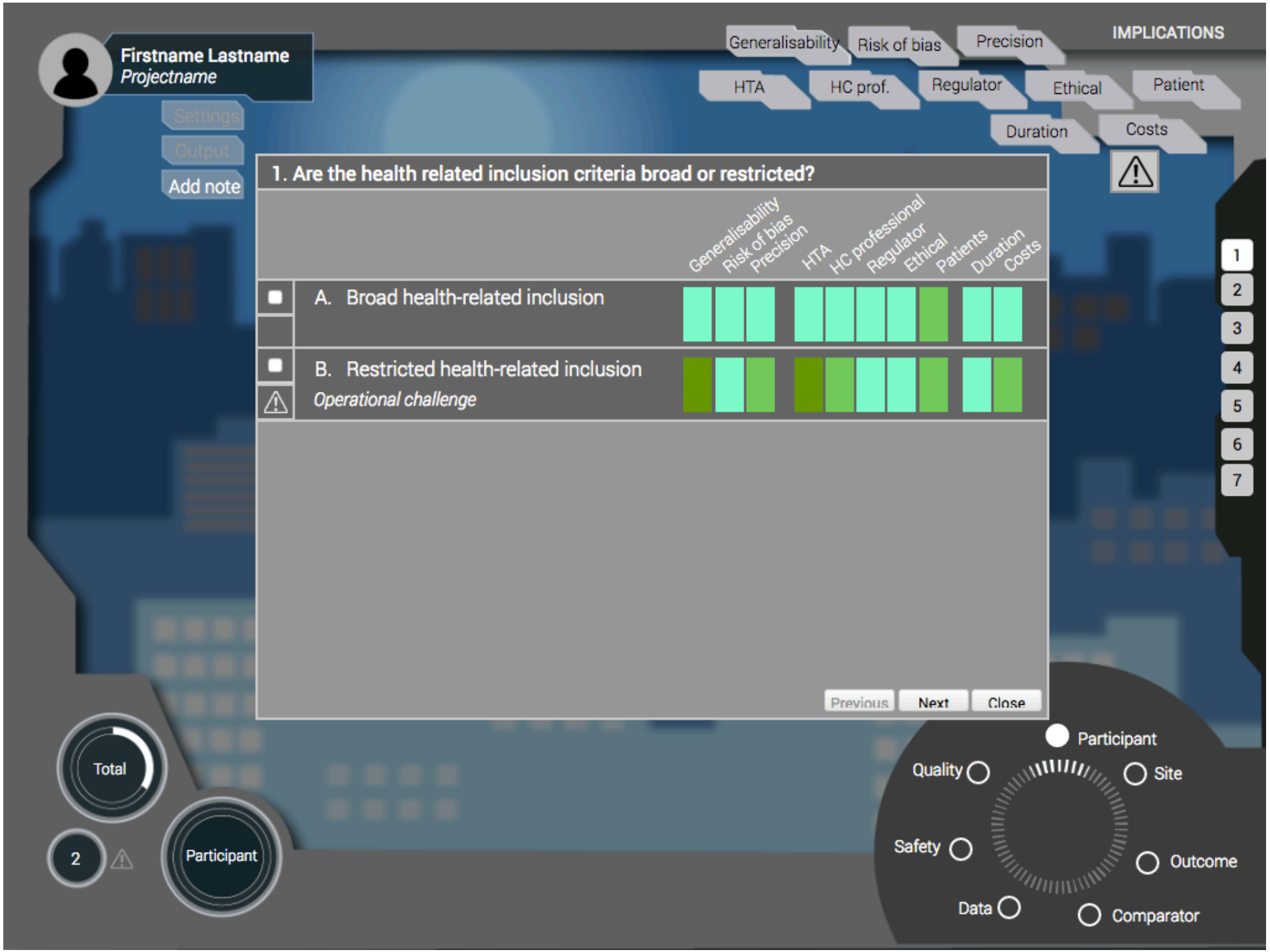
Projectname
Settings
Output
Add note
Generalisability
Risk of bias
Precision
IMPLICATIONS
HTA
HC prof.
Regulator
Ethical
Patient
Duration
Costs
Questions for patient/participant:
1. Are the health related inclusion criteria broad or restricted?
2. Are non-health related inclusion criteria used?
3. Can vulnerable or special patients be included?
4. Are specific subgroups oversampled?
5. Are Strategies used to imrpove recruitment?
6. Are strategies to reduce attrition used?
7. Is the population representative of the study population?
Total
2
Participant
Participant
Quality
Site
Safety
Outcome
Data
Comparator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Add note
Generalisability
Risk of bias
Precision
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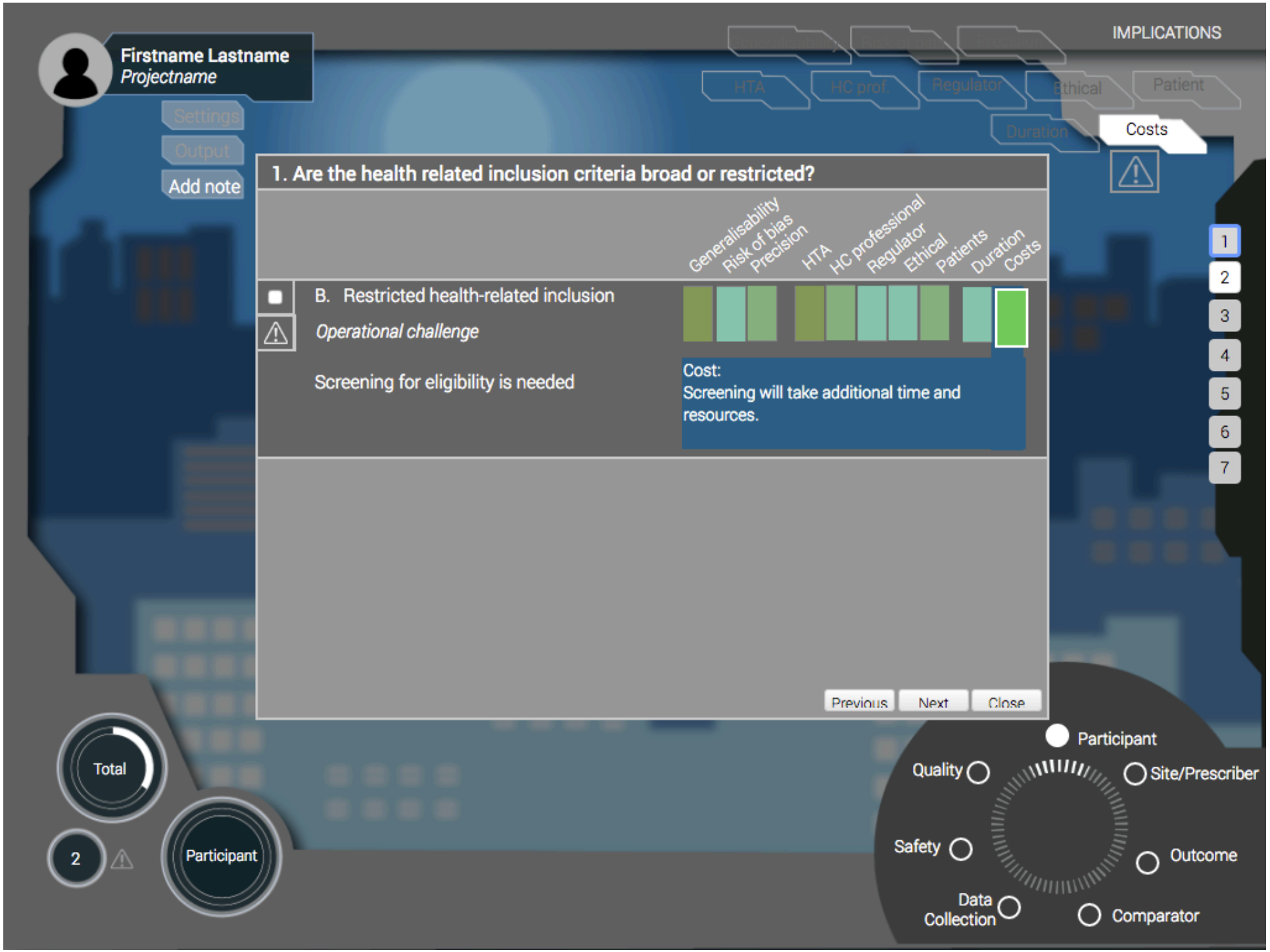
Regulator
Ethical
Patient
Duration
Costs
IMPLICATIONS
1. Are the health related inclusion criteria broad or restricted?
Generalisability
Risk of bias
Precision
HTA
HC professional
Regulator
Ethical
Patients
Duration
Costs
A. Broad health-related inclusion
B. Restricted health-related inclusion
Operational challenge
Previous
Next
Close
1
2
3
4
5
6
7
Total
2
Participant
Participant
Quality
Site
Safety
Outcome
Data
Comparator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IMPLICATIONS
HTA
HC prof.
Regulator
Ethical
Patient
Duration
Costs
1. Are the health related inclusion criteria broad or restricted?
Generalisability
Risk of bias
Precision
HTA
HC professional
Regulator
Ethical
Patients
Duration
Costs
B. Restricted health-related inclusion
Operational challenge
Screening for eligibility is needed
Cost:
Screening will take additional time and resources.
1
2
3
4
5
6
7
Previous
Next
Close
Total
2
Participant
Participant
Quality
Site/Prescriber
Safety
Outcome
Data Collection
Comparator

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In summary

- Research question defines trial design
- Increasing emphasis on generalizability to the real world
- Pitfall: default of explanatory trial
- Design phase: anticipate on operational challenges & their implications
- Tool = decision support tool, NOT decision making tool

- Aim to have first version of tool available early 2017

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END

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